Prospective Observational Study of Retinopathy of Prematurity in a Tertiary Care Hospital, Tirupati

K. Sivaramudu¹, R. Sravya², Y. Mrudula³, B. Manohar⁴, Y. Pradeep⁵

¹Department of Paediatrics, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh. ²Department of Paediatrics, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh. ³Department of Paediatrics, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh. ⁴Department of Paediatrics, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh. ⁵Department of Paediatrics, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh.

ABSTRACT

BACKGROUND
Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative disorder of the retina with abnormal proliferation of blood vessels at the junction of vascular and avascular retina occurring in preterm low birthweight infants. A simple screening test done within a few weeks after birth by an ophthalmologist can avoid this preventable blindness.

METHODS
This is a hospital based prospective observational study done from October 2017 to September 2018 on all babies with gestational age less than 35 weeks and birthweight less than 1750g admitted in NICU, SVRRGH, Tirupati during the study period. The babies were registered by optometrist and taken to the ophthalmologist for detailed evaluation by indirect ophthalmoscopy. Babies with ROP changes were followed up for progression and managed appropriately. Chi-square test is used to find association between ROP and risk factors.

RESULTS
Of the 201 babies included in the study, 23 babies had ROP. Overall incidence of ROP in present study was found to be 11.44%. The mean birth weight (t=2.1188; p=0.03) and mean gestational age (t=4.470, p value <0.0001) was significantly lower in babies with ROP compared to those without ROP. Of the 23 babies, ROP stage-1 was seen in 5 (21.73%), stage-2 in 8 (34.78%), stage-3 in 10 babies (43.47%) and Zone I disease was observed in 1 (4.3%), Zone II in 7 (30.43%) and Zone III in 15 (65.21%) babies was seen. 43.47% of babies with ROP required intervention and underwent laser photocoagulation and were treated successfully without any recurrence on follow up. Common risk factors found in the present study were oxygen-therapy (100%), hyperbilirubinemia (74.1%), RDS (61.7%), sepsis (28.8%), PIH (27.8%), multiple gestation (15.4%) and GDM (2.48%). Among them, oxygen therapy (p =0.000), multiple gestation (p=0.012) and sepsis (p=0.014) were found to be statistically significant risk factors on univariate analysis. On multivariate analysis only oxygen therapy and sepsis were found to be independent risk factors.

CONCLUSIONS
Oxygen should be used as a drug only if there is a specific indication. Oxygen blenders should be used compulsorily. In NICU strict oxygen protocols have to be followed. Attempts should be made to keep PaO₂ between 50-80 mmHg and SpO₂ between 90-93%. Meticulous screening and regular follow up of high risk newborns and timely intervention will prevent morbidity due to ROP.

KEYWORDS
Retinopathy of Prematurity, Low Birth Weight, Preterm, Oxygen Therapy
BACKGROUND

Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative disorder of the retina occurring in preterm low birth weight infants. It features abnormal proliferation of blood vessels at the junction of vascular and avascular retina. This retinal neovascularization may regress completely in 90% cases or leave sequelae from mild myopia to bilateral total blindness in 10%. With the increase in the survival of preterm babies, ROP has become one of the leading causes of preventable childhood blindness throughout the world. A simple screening test done within a few weeks after birth by an ophthalmologist can avoid this preventable blindness. Although screening guidelines and protocols are strictly followed in the developed nations, it lacks in developing economies like India which has the highest number of preterm deliveries in the world. The burden of blindness is set to increase tremendously in the future, if corrective steps are not taken immediately. With 3.5 million preterm births every year and about 15000 ophthalmologists practicing in India each ophthalmologist would need to screen more than 200 preterm neonates every year. Moreover, only a small proportion of ophthalmologists are trained in use of indirect ophthalmoscopy in neonates. This huge demand-supply gap can be met only by technological solutions like use of wide-angle retinal camera, image capturing by trained technicians, and remote image review and reporting by trained ophthalmologists. Despite increasing number of legal cases related to loss of eyesight due to late detection, parents and community in general are unaware about ROP and need of timely screening. Due to patient overload, a large proportion of preterm neonates are discharged home before the screening window starts at 3-4 weeks of postnatal age.

Oxygen-exposure, RDS, Hyperbilirubinemia, Anaemia, Blood transfusions, Multiple gestation, PIH, GDM, Apnoea, Mechanical ventilation, Sepsis are well recognized risk factors for ROP. Breastfeeding is protective against development of ROP. Prevention is still the best strategy available at present to avoid the morbidity due to ROP.

Realizing its importance, Government of India has recently included ROP in the newborn screening program under Rashtriya Bal Swasthya Karyakram (RBSK). The RBSK is a child health screening and early intervention program since 2013, under the National Health Mission. It includes ROP as one of the defects at birth that will be detected at 0-6 weeks of age and also detects and treats children with visual impairment from 0-18 yrs. with proper follow up.

METHODS

This is a hospital based Prospective observational study conducted October 2017 to September 2018 after ethical committee clearance. All babies with gestational age less than 35 weeks and birthweight less than 1750 grams admitted in NICU, SVRRGGH during study period were included in the study.

Inclusion Criteria

A. Babies weighing lesser than 1750 grams.
B. Babies born at less than 35 weeks of gestation.
C. Selected pre-term infants with birth weight between 1750 to 2000 grams or gestational age of more than 35 weeks with sickness like need for cardiorespiratory support, prolonged oxygen therapy, hyperbilirubinemia, anaemia needing blood transfusion, neonatal sepsis.

Exclusion Criteria

Babies with congenital cataracts and congenital retinal Dystrophies.

All babies who require ROP screening according to the inclusion criteria mentioned above were registered on a daily basis by NHM-RBSK-TEIC appointed optometrist bedside and then the babies were taken to the ophthalmologist for detailed evaluation.

The Timing of First Examination

• After 2 weeks of birth for the babies born with birth weight <1000g and/or <28 weeks.
• After 4 weeks of birth for the babies born with birth weight >1000g and/or > 28 weeks of gestation.

All the babies were screened by the trained ophthalmologist using indirect Ophthalmoscope. Depending upon the severity, ROP was classified according to revised International Classification of Retinopathy of Prematurity, published in 2005. The babies with ROP changes will be followed up for progression and managed appropriately. Chi-square test was used to find association between ROP and risk factors.

RESULTS

201 babies who fulfilled the inclusion criterion admitted in neonatal unit of Department of Paediatrics, SVRRGH, Tirupati between October 2017 to September 2018 were enrolled and then screened by the ophthalmologist. Of the 201 babies included in the study, 23 babies had Retinopathy of prematurity. Overall incidence of ROP in present study was found to be 11.4%. Clinical characteristics of the babies screened were as follows:

Of the 201 babies studied, 109 (54.22%) were male and 92 (45.77%) were female. Mean birth weight of babies with ROP is 1348.7g (+SD215.67) (range-1050 to1730 g) and without ROP was 1495.11g (+SD321.81). The mean birthweight was significantly lower in babies with ROP compared to those without ROP (1348.7g vs. 1495.11g) with t=2.1188; p=0.04. The mean period of gestation of babies with ROP was 30.52wk (+SD1.62) and without ROP was 32.52(+SD2.075). The mean period of gestation was significantly lower in babies with ROP compared to those
without ROP (30.52 weeks vs 32.52 weeks) with t=4.470; p value <0.0001.

We considered the presence or absence of 8 risk factors. In our NICU, considering the cohort of all babies the common risk factors were oxygen therapy (100%), Neonatal hyperbilirubinemia (74.1%), Twins(15.4%), RDS(61.7%), Sepsis(28.8%), Pregnancy induced hypertension(PIH) (27.8%) and Gestational diabetes mellitus (GDM) (2.4%). Among them Oxygen therapy (p =0.000), multiple gestation (p=0.012) and sepsis (p=0.014) were found to be statistically significant risk factors on univariate analysis. On multivariate analysis only oxygen therapy and sepsis were found to be independent risk factors. Hyperbilirubinemia (p=0.802), PIH (p=0.220), anaemia & blood transfusions (p=0.497), RDS (p=0.651) and GDM (p=1.00) were not found to be statistically significant risk factors.

Staging of ROP
Out of the 201 babies, all the babies who had retinal vessels reaching up to mid zone 3 were considered mature. 23 babies had some changes of ROP. No babies had Aggressive posterior ROP. We did not find anterior segment involvement in any of our babies.

Classical ROP
ROP stage1 was seen in 5 babies (21.73%), stage 2 in 8 babies (34.78%) and stage 3 in 10 babies (43.47%). 43.47% (10 babies) with classical ROP met the threshold for treatment based on ETROP guidelines and received laser photocoagulation. Of the 23 babies with ROP, Zone I disease was observed in 1(4.3%) babies, Zone II in 7(30.43%) babies and Zone III in 15(65.21%) babies.

Treated ROP
10 babies, reached threshold for treatment during screening. All of them were referred to higher centers and were treated with 532nm green laser using indirect opthalmoscopic delivery system. All babies had favorable outcome after laser treatment (100%). Favorable outcome was defined using CRYO-ROP guidelines.

**DISCUSSION**

201 babies were screened from October 2017 to September 2018. In the present prospective observational study with the screening criteria of <1750g at birth and gestational age <35 weeks and >35 weeks with risk factors reports the incidence of ROP as 11.44% which is lower than the previous Indian studies like Saravanan Jothi et al(54.8%) and higher than Crystal Le et al(2.3%). Significantly lower incidence may be explained by the fact that the study included extremely premature infants also and very low birth weight infants and loss of such infants due to death in present study.

Crystal Le et al in 2016 did a study which revealed an incidence of 2.3% which is much lower than present study. This lower value may be due to the small sample size of study as well as a result of the patient population at the NICU. This particular NICU is in collaboration with an eye institute and abides by strict oxygen therapy and ROP screening guidelines, which is likely responsible for the low incidence of ROP development. The hospital is an urban institution that serves predominantly un-insured patients of an average income group. As a result of these factors, many infants born at this facility presented with less prenatal risk factors and subsequently, an overall reduced incidence of disease.

Present study included the babies with Birth Weight <1750g and period of gestation <35 weeks and mean Birth Weight and period of gestation are 1478.35g (±SD14.566) and 32.28 weeks (±SD2.122) respectively. The mean GA of babies with ROP in present study is comparable to most of the recent studies like Anoop Mantri et al (32.83 ±1.65 weeks) and slightly higher than Crystal Le et al (31 weeks), Deepali Gawai et al (30 weeks). The mean Birth Weight of present study is higher than Anoop Mantri et al (1340±210 g), Kumar N et al(1043.75 g) and lower than Saravanan Jothi et al (1495 g), Vinekar et al(1533.9±286 g).

Aggressive posterior retinopathy of prematurity (APROP) is a severe form of zone 1 ROP, has been reported to be an important part of ROP in Indian studies. In our study we did not have babies with APROP. Present study had 100% favourable outcome and followed the ETROP guidelines and is comparable with Lira et al (96.7%) and Sanghi G(97%).

Risk Factors
Present study looked for risk factors in babies as previously done in other ROP studies. Comparison of incidence of all risk factors between the group that had ROP and the group that did not have ROP was done. This was compared with other studies. Oxygen therapy, multiple gestation and sepsis are significant risk factors and strongly associated with ROP. In a study by Kumar N et al, on univariate analysis birth weight, gestational age, oxygen administration, RDS, sepsis, exchange transfusion and mechanical ventilation were found to be significant factors. In another study by Anjali Parekh et al, in case of severe ROP on univariate analysis we found that the higher incidence of risk factors such as ventilation, anaemia requiring blood transfusion, apnoea and seizures were significant determinants of severe ROP (P-value<0.05 for all). In a study done by Crystal Le, the most prevalent risk factors among patients with ROP are RDS (58%) and use of oxygen therapy (71%). In Saravanan Jothi et al study, RDS, oxygen therapy and sepsis were found to be risk factors. Multiple gestation was found to be significant risk factor with p value 0.012 which was comparable with Sood et al study. ROP in multiple gestation is mostly related to prematurity and low birth weight.

Sepsis (p=0.014) was also a statistically significant risk factor and present study correlates with various other studies like kumar N et al, Saravanan Jothi et al, Anoop Mantri et al, Crystal Le et al, Deepali Gawai et al. Sepsis increases the oxygen demand and interfere with oxygen tension, which might increase retinal ischemia, resulting in ROP.
On multivariate analysis of the three significant risk factors in present study, oxygen therapy and sepsis were found to be independent risk factors which were statistically significant. Other risk factors like Hyperbilirubinemia, Anaemia requiring blood transfusions, RDS, PIH and GDM were found to be statistically insignificant in present study.

The overall incidence of ROP as 11.44%. All the babies with BW<1750g and/or GA <35 weeks and babies with risk factors but more than 35 weeks and between 1750- 2000 g were also screened. The mean birth weight was significantly lower in babies with ROP compared to those without ROP (1348.7 g vs 1495.11 g) with t=2.1188; p=0.0353. The mean gestational age was significantly lower in babies with ROP compared to those without ROP (30.52 weeks vs. 32.52 weeks) with t=4.470; (p value <0.0001). Of the 23 babies, ROP stage 1 was seen in 5 babies (21.73%), stage2 was seen in 8 babies (34.78%) and stage3 was seen in 10 babies (43.47%). Of the 23 babies with ROP, Zone I disease was observed in 1 (4.3%) baby, Zone II in 7 (30.43%) babies and Zone III in 15 (65.21%) babies. 4(2%) babies with BW >1500 g had ROP. 11 (5.4%) babies with ROP were >30 weeks of GA and 2(1%) babies with ROP was>32 weeks of GA. 43.47% of babies with ROP required intervention and underwent laser photocoagulation and were treated successfully without any recurrence on follow up. Common risk factors found in present study were oxygen therapy (100%), hyperbilirubinemia (74.1%), RDS (61.7%), sepsis (28.8%), PIH (27.8%), multiple gestation (15.4%) and GDM (2.48%). Among them Oxygen therapy (p =0.000), multiple gestation (p=0.012) and sepsis (p=0.014) were found to be statistically significant risk factors on univariate analysis. On multivariate analysis only oxygen therapy and sepsis were found to be independent risk factors.

Limitations
The sample size is small and may not represent all premature babies in this region. Hence, a larger multi-centric study over a longer duration of period is required to establish the true incidence and causal relationship of risk factors associated with ROP in a developing country like India. Follow up was done till 40 weeks of age only. Lack of long term follow up to assess future ophthalmological sequelae including myopia, cataract, squint and other long term complications associated with ROP.

CONCLUSIONS
O_{2} should be used as a drug, and should be used only if there is a specific Indication. Oxygen blenders should be used. Attempts should be made to keep PaO_2 between 50-80 mmHg and SpO_2 between 90-93%. Hourly measurement and recording of oxygen delivered to the premature infant and calibration of oxygen analyser with room air and 100% O_2 should be done at least eight hourly. Telemedicine approach using Retcam allows large coverage area of ROP screening program in the country which can help in coping up of huge demand and supply gap. Meticulous screening and regular follow up of high-risk newborns and timely intervention will prevent morbidity due to ROP. There is a need for the obstetricians, paediatricians and ophthalmologist to work as a team to prevent blindness due to ROP.

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REFERENCES

