REVIEW ARTICLE

Retinopathy of Prematurity: AIIMS, New Delhi Experience

SINDHU SIVANANDAN, *PARIJAT CHANDRA, ASHOK K DEORARI AND RAMESH AGARWAL

*From Division of Neonatology, Department of Pediatrics, and *Department of Ophthalmology, Dr RP Centre for Ophthalmic Sciences; All India Institute of Medical Sciences, New Delhi, India.*

Correspondence to: Dr Ramesh Agarwal, Additional Professor, Division of Neonatology, Department of Pediatrics, (Newborn Health Knowledge Center (NHKC), ICMR Center for Advanced Research in Newborn Health and WHO Collaborating Centre for Newborn Training and Research, New Private Ward-1st Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. ra.aiims@gmail.com

Retinopathy of prematurity (ROP) is a leading cause of potentially avoidable childhood blindness worldwide. With improvement in neonatal care, more preterm infants are surviving with a resultant increase in the number of ROP cases. In low-middle income countries, the disease epidemiology is characterized by the occurrence of ROP at higher birthweight in premature babies with greater severity at presentation. In this article, we describe the ROP screening and management program at the All India Institute of Medical Sciences (AIIMS), New Delhi that has evolved over last three decades. The AIIMS model demonstrates that with high-quality perinatal – neonatal care and a stable ROP program, severe ROP is a preventable disease in bigger preterm neonates (28 weeks or higher gestation) and largely remains a disease of extremely low gestational age babies- a phenomenon similar to that noted in high-income countries.

Keywords: *Blindness, Preterm, Quality of care, Situational analysis.*

Retinopathy of prematurity (ROP) is a leading cause of potentially avoidable childhood blindness worldwide. With improvement in neonatal care, more preterm infants are surviving with a resultant increase in the number of ROP cases globally. However, there is a gross disparity in the incidence of ROP between low- and middle-income countries (LMIC) and high-income countries (HIC). Severe ROP is defined as ROP stage 3 to 5 by some authors while others have defined it as ROP requiring treatment [1]. The reported incidence of severe ROP from HIC range from 12.5% in England [2] (1990-2011), 12.7% in Canada [3] (2003-2010) to 16% in USA [4]. In LMIC, the incidence of ROP is variable (3 to 44%) depending on the survival rates of preterm infants and the quality of neonatal care [1]. Among HIC with universal access to high quality neonatal care, ROP is predominantly a disease of extremely preterm babies (<28 weeks gestation and birth weights <1250 grams) whereas the disease occurs in infants of higher gestation and birth weight in LMIC [1]. Lower gestational age and birth weight and exposure to supplemental oxygen are the most consistently identified risk-factors for occurrence of ROP.

In LMIC, many neonatal units caring for preterm babies lack adequate resources such as air-oxygen blenders, pulse oximetry and optimum nursing care. Traditional bedside ROP screening performed in the NICU is logistically difficult as trained ophthalmologists may be unavailable thereby mandating referral of these infants to an ophthalmic center for screening and or laser therapy. These challenges in LMIC need to be overcome in order to provide optimum care. In this article, we describe the neonatal care services and the ROP screening and management program at AIIMS that has evolved over last three decades. The AIIMS model of care shows that it is possible to run a successful collaboration between neonatology and ophthalmology teams, and achieve low rates of ROP incidence despite high survival rate of vulnerable babies.

NEONATAL SERVICES AT AIIMS

Currently, AIIMS runs a 10-bedded level-III and a 20-bedded level-II NICU in addition to several kangaroo-care and rooming-in beds. There are about 2600 deliveries annually, majority of them being high-risk pregnancies. Approximately, 35 to 40% neonates born to these mothers require NICU admission. Currently five faculty members, 7 neonatology fellows pursuing super specialty training in Neonatology, 2 pediatrics senior residents, 6 pediatric junior residents and approximately 60 neonatal nurses make up the team. All deliveries are conducted and attended by resident doctors. The nurse-patient ratio is 1:1 to 1:2 in the Level-III unit and 1:2 to 1:3 in the level-II unit. The obstetric perinatal care services have facilities for antenatal diagnosis, fetal monitoring and fetal intervention. Neonates discharged home are seen either in the high-risk follow up clinic (HRC) or in the well-baby

clinic. The HRC has a dedicated team of physicians, clinical psychologist, physiotherapist, early interventionist, dietician and a medical social worker under one roof. Ophthalmology and hearing services function in separate areas. The improvement in neonatal care is reflected in the improving survival of neonates in recent years. The overall neonatal mortality rate (NMR) of babies born at AIIMS has declined from 38 per 1000 live births in 1983 to 15 per 1000 live births in 2000. Despite dealing with high-risk cases in 2014 and 2015,the NMR at AIIMS was 13.7 and 11.4 per 1000 live births while the national figures for the same years were 29 and 28/1000 live births, respectively [5].

Survival and Morbidity in Recent Years

With advances in neonatal care, the survival of extremely low birth weight (ELBW; <1000 grams) neonates has improved dramatically. These neonates are at increased risk of morbidities like ROP, chronic lung disease, cerebral palsy and neurodevelopmental impairment. Over the last decade, the total number of live births at AIIMS has steadily increased and the percentage of neonates <32 weeks of gestation at higher risk of morbidities related to prematurity has remained relatively constant. During this period the survival of extremely preterm neonates (<28 weeks gestation) has steadily increased from 31.3% (2001-2002) to 69.7% (2013-2014). Similarly, the survival of ELBW infants, which include babies who are small for gestation or having intra uterine growth restriction, has increased from 48% (2001-2002) to 66.7% (2013-2014). We incorporated potentially best clinical practices over time in our NICU such as gentle ventilation at birth with the early use of continuous positive airway pressure (CPAP), adherence to oxygen saturation norms at birth with the use of pulse oximeter, delayed cord clamping at birth, attention to thermoregulation with the use of plastic bags/ cling wrap and transport incubator, preferential use of non-invasive ventilation strategies in the NICU, peri-extubation use of caffeine, strict hand hygiene policy, exclusive use of mother's own milk, kangaroo care, developmentally supportive care and parental involvement in neonatal care. Our nurse-patient ratio has also improved over time as well as our antenatal steroid coverage rates.

CHANGING PROFILE OF ROP AT AIIMS

AIIMS initiated its ROP program way back in 1990, one of the earliest in the country, and the program has evolved over the years since then. The program started with a regular ROP screening day conducted in the AIIMS NICU once a week. We describe four time periods (1992-94, 1999-2000, 2003-2008, 2009-2013; corresponding to three publications [6-8] with the data for the latest period from our statistics, during which the screening criteria and indications for treatment and type of treatment has evolved. What is common to the periods is strict compliance to screening guidelines, universal screening of all "at risk" population, in-house or bedside screening and management of admitted neonates. Readers should note that AIIMS NICU is an exclusive inborn unit and all the data pertain to inborn neonates only. The data pertaining to the four periods are summarized in ***Table* I**.

Period I: In an observational study [6] undertaken at AIIMS over a 15-month period between 1992-94, 66 infants were screened and completed the follow up for ROP. Infants were screened if they were <35 weeks gestation or <1500 grams at birth. Preterm infants who required oxygen therapy for more than 24 hours also underwent ROP screening. The first clinical examination was done at 2 weeks of age and repeated every 2 weeks

TABLE I TREND OF ROP OVER THE YEARS

Characteristics	*Period I (1992-94)*	*Period II (1999-2000)*	*Period III (2003-2008)*	*Period IV (2009-2014)*
Screening criteria	Gestation <35 wk or <1500 g at birth	Same as period I	Gestation ≤32 wk or birth weight ≤1500 g	Same as Period III
Treatment criteria	As per CRYO ROP[8] criteria	Similar to period I	As per ETROP [9] criteria. CRYO ROP until 2005	Similar to Period III
Infant screened (*n*)	66	76	704	754
Any ROP, No. (%)	13/66 (20)	24/76 (32)	84/704 (11.9)	151/754 (20)
Threshold ROP or severe ROP, No. (%)	6/66 (9)	2/76 (2.6)	33/704 (4.7)	35/754 (4.6)
Incidence of ROP among <1000 g, No. (%)	4/6 (67)	4/12 (33)	41/125 (32.8)	30/110 (27)

until discharge and thereafter every 4 weeks until 42 weeks post-menstrual age, when retinal vascularization is complete. Infants with threshold ROP underwent cryotherapy. During this period, the incidence of any ROP and threshold ROP was 19.6% (13/66) and 9% (6/66), respectively. Both the incidence and the severity were inversely related to gestation and birthweight. The incidence of ROP in infants with a birthweight <1500 g and <1000 g was 27% (10/37) and 67% (4/6), respectively. The authors examined a large number of potential risk factors for their association with ROP and noted blood transfusion and clinical sepsis as independent risk factors [6].

Infants with threshold ROP underwent cryotherapy using a cryoprobe with scleral indentation. In the first patient, the procedure was performed in the ophthalmic operation theatre under general anesthesia but further procedures were done in NICU with a portable cryotherapy apparatus using morphine for sedation and systemic analgesia, pancuronium for neuromuscular paralysis and lignocaine drops for local anesthesia. After cryotherapy, the infants were followed up every week to ascertain regression of the disease. Most complications of the procedure were minor and self-limiting, and involved congestion, lid edema and chemosis. Major complications like bradycardia, corneal edema, and vitreo-retinal hemorrhage were less frequent. Follow up clinical examinations and posterior fundus photographs showed regression of ROP in all the treated eyes. Five eyes (56%) showed a favorable structural outcome while the other 4 eyes (44%) showed an unfavorable outcome (defined as the presence of posterior retinal folds or a retinal detachment involving zone I of the posterior pole or retrolental tissue obscuring the visualization of the posterior pole).

Period II: During the period between 1999-2000 [7], similar screening criteria as described in period I were followed. During this period, 76 infants were screened. A higher proportion of infants in the second period compared to the first period, respectively, had a lower gestational age (<33 weeks, 84% *vs*. 53%) and birth weight (<1500 g, 74% *vs*. 56%). The incidence of risk factors was not significantly different between two periods. A total of 24/76 (31.5%) infants developed ROP in this period compared with 13/66 babies (20 percent) in the previous period. The incidence of threshold ROP requiring treatment among those screened, showed a significant decrease from an initial 9% (6/66) to only 2.6% (2/76) in the second period. Therapy for threshold ROP was successful in achieving regression in all treated infants. Among infants <30 weeks gestation and <1000 grams at birth, the incidence of ROP decreased from 63% to 37%, and 66% to 33%, for period 1 *vs*. period 2, respectively, although not reaching statistical significance. Apnea, sepsis and male sex were identified as independent risk factors for ROP. Between the two periods, although the incidence of any ROP was similar, the more severe form of the disease (stage III and threshold ROP) showed a downward trend. The authors conjectured that this decrease could be related to increased awareness about risk factors for ROP and improved standard of neonatal care.

Period III (2003-2008): In this retrospective study [8] done during the period 2003 to 2008, ROP screening was done on all neonates with gestation ≤32 weeks or birthweight ≤1500 g. Infants with birth weight of 1501 to 1800 g or gestation of 33-34 weeks were also screened in the presence of additional risk factors like need for oxygen or mechanical ventilation. During this study period, 704 infants were screened for ROP. The mean birth weight and gestation of the infants screened were 1335 g and 31 weeks, respectively. After the year 2005, ROP treatment was based on Early Treatment of Retinopathy of prematurity (ETROP) guidelines [9].

ROP was diagnosed in 11.9% (84/704) infants, and 4.7% (33/704) had severe ROP requiring laser therapy. The mean (SD) birthweight and gestation of infants with severe ROP was 1113 (436) g and 29(2.7) wk, respectively. The incidence of any ROP in ELBW infants was 32.8% (41/125) while severe ROP requiring laser therapy was seen in 14.4% (18/125) infants. ELGA infants were at a high risk (61%, 24/39) of developing any ROP and 28% (11/39) had severe ROP requiring laser therapy. By multivariate logistic regression the authors identified respiratory distress syndrome, PDA requiring medical or surgical treatment, and meningitis as independent risk factors for severe ROP.

Period IV (2009-2014): During this period, the screening protocol was similar to that of period III. In this period, 754 infants were screened, and ROP of any stage was diagnosed in 20% (*n*=151) infants; 4.6% (*n*=35) of those screened had severe ROP requiring laser therapy. During this period, the survival of extremely low gestational age infants increased dramatically from 39% in 2009 to 2010 to 70% in 2013-2014. However, the incidence of ROP requiring therapy remained constant at 4.6% in spite of more at-risk neonates surviving. This could be attributed to improved neonatal care practices.

SPECTRUM OF ROP AT AIIMS COMPARED TO OTHER CENTERS

The incidence of ROP at other centers from India *viz*. (PGIMER, Chandigarh [10,11], Child Trust Hospital, Chennai [12], St Stephen's hospital, Delhi [13], LV Prasad

Eye Institute, Hyderabad [14] and RL Jalappa Hospital, Karnataka [15]), varies between 38% [12] to 57% [13] depending upon the center and the screening criteria used (***Web Table* I**). The incidence of any ROP at AIIMS was 20% in 1992-93 and 11.9% in 2003-08. The incidence of severe ROP was less; 9% in 1992-93 and 4.7% in 2003-08. At AIIMS, with increased emphasis on improving quality of neonatal care with trained and skilled nurses, we saw a dramatic decline in any ROP as well as ROP requiring laser over the years. However, our data cannot be directly compared with data from other centers, because most other studies have included outborn neonates as well as babies referred to ophthalmologists for screening and treatment of ROP.Moreover, the difference in ROP between various centers could be attributed to differences in the screening criteria, quality of neonatal services, and referral bias. Blencowe, *et al.* [16] estimated the global ROP burden from population-based incidence of ROP from 2000 to 2010 in countries with both low and high NMR. The meta-analyses of 42 studies from 23 countries with NMR ≤5 suggested that 36.5% (95% CI: 31.8-41.4%) of all survivors <32 wks developed some degree of ROP and approximately one-third of them would progress to type 1 disease. Among survivors between 32-36 wksgestational age, 7.7% developed any ROP; out of which, 11% progressed to type I disease requiring treatment.

LESSONS LEARNT AT AIIMS

Implementation of a ROP Screening Policy

The successful reduction of severe ROP in spite of increased survival of high-risk neonates could be attributed to better neonatal care practices as well as the adoption and universal implementation of ROP screening policy at AIIMS. All neonatal units caring for at-risk neonates should have a ROP-screening policy based on National guidelines and should be 100% compliant with it. Although many LMIC including India (National Neonatology Forum guidelines) have national guidelines (*e.g.*, Brazil [17], Argentina, Chile, Ecuador, El Salvador, Peru [18], China [19, 20] , Russia and Mexico [21]), only a few units implement them. In a study from Mexico [21] involving 32 NICU in five of the largest states, only 10 (31.2%) had fully compliant programs and 11 (34.4%) had no program despite having National guidelines. In the remaining 11 (34.4%), different screening criteria were used, screening was not undertaken in the NICU or was undertaken by a neonatologist and/or bevacizumab was used as the first-line treatment

In a telephonic survey of 234 pediatricians from six states in India, although all respondents were aware of ophthalmic complications of preterm birth including ROP, only 135/234 (58%) got at-risk neonates screened for ROP either in their own center or referred to an ophthalmologist working elsewhere [22]. Eighty (34%) pediatricians did not refer at all, and 19 (8%) referred only sometimes depending upon the availability of a trained ophthalmologist. Non-availability of trained ophthalmologists in hospitals with neonatal services is a major deterrent in effective screening of at-risk neonates. Hence, for a program to be successful, commitment to implementation and universal screening are essential.

ROP Screening Guidelines

The American Academy of Pediatrics recommends ROP screening for babies ≤1500 g birth weight or ≤30 weeks gestational age and those infants >1500 g or >30 wk with an unstable clinical course or at high risk for ROP [23]. As per the Canadian guidelines, ROP screening is recommended for GA of ≤30 wk or birthweight ≤1250 g [24] and the United Kingdom recommends screening for <32 week or <1501 g [25]. In India, the National Neonatology Forum (NNF) recommends that screening for ROP should be performed in all preterm neonates who are <34 weeks gestation and/or <1750 grams birth weight. Apart from these infants, those preterm infants between 34 to $36^{6/7}$ weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP should also be screened. The guideline from China recommends screening for neonates ≤34 wks or BW ≤2000 grams [26], the guidelines from Brazil [17] and South Africa [27] includes neonates ≤32 wks and ≤1500 grams. The guideline from Latin America recommends screening ≤32 wks or ≤1750 grams [18].

Thus we note that while the high-income countries utilize lower gestation/birthweight cut-off for screening, the LMIC have recommended screening in higher gestation/birthweight babies reflecting a different level of quality of care in the two settings. Our screening criteria in 1990 included preterm neonates <35 week gestation or <1500 gram at birth. Infants requiring oxygen therapy for more than 24 hours or a stormy postnatal course also underwent ROP screening. However, with improvements in neonatal care we have narrowed our screening criteria to include neonates <32 wk gestation and or <1500 g birthweight. We screen preterm infants with birthweight between 1500 and 2000 g or gestation more than 32 wk if they have a turbulent postnatal course like cardio-respiratory instability, prolonged oxygen therapy, repeated episodes of apnea and neonatal sepsis. Our experience at AIIMS suggests that as the quality of neonatal care improves (even in a LMIC setting), severe ROP becomes essentially a disease of extremely preterm babies and is largely preventable in bigger preterm babies similar to that

in high-income countries. A study by Zin, *et al*. [28] from seven neonatal units in Rio showed that survival rates among VLBW neonates could be used as a proxy for screening criteria. They noted that units where survival of VLBW neonates was ≥80%, the screening could include <1500 g or <32 weeks; but for NICU with lower VLBW survival rates, the appropriate screening criteria would be <1500 g or <35 week.

While agreeing that most units should continue to use higher gestation/birth weight cut off, we would like to highlight AIIMS experience that with good quality of care ROP requiring treatment becomes a disease of ELGA babies and screening criteria can be narrowed similar to high-income countries. Therefore, units venturing into a ROP *program* need to keep this lesson in mind. They should consider the rate of severe ROP as a quality-of-care parameter, track data pertaining to screening and management of babies, and amend screening criteria as the situation evolves with time.

A number of factors in addition to screening played a role in the reduction of incidence of ROP at our hospital. These are summarized in ***Box* 1.** Those pertaining to ROP screening and management are discussed below.

a) Implementation of ROP Screening Program

ROP screening requires skilled ophthalmologists who are specially trained to detect and treat ROP, infrastructure investment, coordination, planning and above all teamwork between ophthalmologist and neonatal physician. Our screening procedures are discussed in detail in our ROP protocol and are similar to other published guidelines [14].

BOX 1 FACTORS RESPONSIBLE FOR REDUCED ROP INCIDENCE AT AIIMS

1. Antenatal steroids for eligible pregnant mothers
2. Evidence-based delivery room management
   - Initiate resuscitation with low oxygen concentration (21-30%) using blenders
   - Early use of nasal CPAP
   - Use of pulse oximetry to target oxygen saturations
3. Gentle ventilation strategies
4. A written protocol for management of respiratory distress in preterm neonates
5. Target oxygen saturation between a narrow range and set alarm limits in pulse oximeter
6. Early aggressive parenteral nutrition in ELBW neonates
7. Prevention of nosocomial sepsis
8. Restrictive blood transfusion guidelines
9. Family-centered care
10. A written unit policy for screening and management of ROP

Inborn neonates are screened in the NICU with indirect ophthalmoscopy once a week. A half-day weekly ROP clinic functions at the Level II NICU and is run by the ophthalmology and neonatology teams. Neonates who are discharged home from NICU but require continued ROP screening attend the ROP screening clinic. The neonatal team helps in follow-up care of these neonates namely growth, nutrition, vaccination and developmental screening. The accessories for ROP screening, namely the pediatric eye speculum and scleral indentors are autoclaved and a separate set is used for each neonate. The antenatal and postnatal characteristics and risk factors of each neonate who are screened for the first time are entered into a form. The form is updated until the infant completes follow up. If the infant receives treatment, the details are also noted. Laser photocoagulation, if needed, is performed in the NICU by the ophthalmology team.

CAPACITY-BUILDING

An important aspect of implementing a ROP screening program or any policy is education and training of all stakeholders. AIIMS has taken a leadership role in spreading ROP awareness, and training among pediatricians and ophthalmologists across India for last 20 years. The Dr Rajendra Prasad Centre for Ophthalmic Sciences (RPC) hosted the second International World ROP Congress in New Delhi in November 2009, which helped spread ROP awareness, and encouraged more ROP research in India. RPC collaborated with Sightsavers India in Phase I (2008-2010) to conduct 12 workshops across India with the goal to spread awareness about ROP and encourage pediatricians and ophthalmologists to start ROP screening programs. Six hundred and fifty pediatricians and ophthalmologists were sensitized during this exercise. In Phase 2 (2012-2015) of the project, 8 eye care centers across India were mentored to take leadership role and train pairs of pediatricians and ophthalmologists to start new screening centers across India.

A meeting of all Regional Institutes of Ophthalmology representatives was hosted under the aegis of National Program of Control of Blindness, Ministry of Health in 2013, for these institutions to take leadership role for ROP services in their region. We also hosted the National ROP Summit in 2013 supported by Queen Elizabeth Diamond Jubilee Trust UK, Ministry of Health and Family Welfare and Public Health Foundation of India, which has now

LESSONS LEARNT IN SCREENING AND MANAGEMENT OF ROP

1. An organized ROP screening and management program is possible and can run successfully if objectives, roles and responsibilities are defined. A unit screening policy that is written down and 100% adhered to forms the backbone of ROP program
2. With improved perinatal and neonatal care, significant ROP is primarily a disease of extremely low gestational age babies. Initial screening criteria can be broad and later narrowed down to more preterm babies as quality of care improves.
3. Regular audit of ROP screen and treatment program can help in understanding the main risk factors that need attention.
4. Quality initiatives can help to address the gaps in care by involving the health care workers at all levels through PDSA cycles. Currently, we have QI initiatives targeted at improving delivery room care, exclusive breast milk feeding, kangaroo mother care and oxygen saturation targeting in our NICU.
5. Provision of adequate analgesia is essential during screening procedure and laser therapy. We need to find optimum solutions that can be employed safely in LMIC settings.

culminated in an ambitious funded plan to develop and support ROP services across India in the next few years.

A new high-dependency neonatal unit has recently been established at the Dr Rajendra Prasad Centre for Ophthalmic Sciences (RPC) to allow us to extend the ROP services to the large number of outborn babies referred to the center for screening and or management of ROP.

Future challenges: Once systems are in place to detect and treat ROP early, the future challenge lies in primary prevention of the disease in preterm neonates. This can be done only through improving the quality of neonatal care provided in the NICU. Tighter control of oxygen delivered to neonates can reduce ROP further. When systems for delivering oxygen in varying amounts (blenders) and equipments for measuring oxygen levels in the blood (pulse oximeters) are available, the staff members need to understand the importance of targeting oxygen saturations within a narrow range. A quality initiative effort in our NICU involving preterm neonates on supplemental oxygen by implementing a unit policy on oxygen saturation targeting through staff education led to an increase in time spent in target saturations from a baseline of 66% to 77%, and decrease in time spent in hypoxia. As ROP is caused by multifactorial etiologies, a unit working towards ROP reduction should also focus on hand hygiene, reduction of nosocomial infections, strict adherence to blood transfusion guidelines, gentle resuscitation and early CPAP in the delivery room, and non-invasive ventilation in the NICU. We are also working towards exclusive breast milk feeding by encouraging breast milk expression within six hours of delivery of an extremely preterm neonate.

SCREENING AND LASER TREATMENT FOR OUTBORN INFANTS

The ROP services for outborn babies referred to AIIMS started to grow alongside the ROP screening program that was established for inborn babies since 1990. As the number of babies referred for services continued to increase, a regular ROP clinic was started once a week by a single Retina unit in the year 2000. As numbers continued to rise, both Retina units started running the ROP clinics twice weekly since 2012. The availability of Retcam (a wide angle paediatric retinal imaging system) to document retinal images for follow-up, training and patient counselling; state of the art indirect laser delivery machines and advanced vitreoretinal surgical setup allows us to perform quality laser treatment and give world-class surgical results. A dedicated NICU backup and experienced anaesthesia support is an added advantage.

Contributors: SS: Compiled and analyzed the data and wrote the initial manuscript; PC: Provided critical insight, wrote manuscript and also revised it; AKD: Provided insight and guidance, helped in writing the manuscript and revised the final manuscript; RA: Provided insight and guidance on writing, revised the manuscript and shall act as the final guarantor for the manuscript.

Funding: None; *Competing interest*: None stated.

REFERENCES

REFERENCES

1. Zin A, Gole GA. Retinopathy of prematurity-incidence today. Clin Perinatol. 2013;40:185-200.
2. Painter SL, Wilkinson AR, Desai P, Goldacre MJ, Patel CK. Incidence and treatment of retinopathy of prematurity in England between 1990 and 2011: database study. Br J Ophthalmol. 2015;99:807-11.
3. Thomas K, Shah PS, Canning R, Harrison A, Lee SK, Dow KE. Retinopathy of prematurity: Risk factors and variability in Canadian neonatal intensive care units. J Perinatal Med. 2015;8:207-14.
4. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, *et al*. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126:443-56.
5. The World Bank. Neonatal Mortality Rate. Available from: *http://data.worldbank.org/indicator/SH.DYN.NMRT*. Accessed March 12, 2016.
6. Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari HK. Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J India. 1996;9:211-4.
7. Aggarwal R, Deorari AK, Azad RV, Kumar H, Talwar D, Sethi A, *et al*. Changing profile of retinopathy of prematurity. J Trop Pediatr. 2002;48:239-42.
8. Kumar P, Sankar MJ, Deorari A, Azad R, Chandra P, Agarwal R, *et al*. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. Indian journal of pediatrics. 2011;78:812-6.
9. Early Treatment For Retinopathy Of Prematurity Cooperative G. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Archives of ophthalmology. 2003;121:1684-94.
10. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol. 1995;43:123-6.
11. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J Ophthalmol. 2007;55:331-6.
12. Gopal L, Sharma T, Ramachandran S, Shanmugasundaram R, Asha V. Retinopathy of prematurity: a study. Indian J Ophthalmol. 1995;43:59-61.
13. Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity. experience in a large maternity unit with a medium size level-3 nursery. Indian J Ophthalmol. 2001;49:187-8.
14. Jalali S, Anand R, Kumar H, Dogra MR, Azad R, Gopal L. Programme planning and screening strategy in retinopathy of prematurity. Indian J Ophthalmol. 2003;51:89-99.
15. Hungi B, Vinekar A, Datti N, Kariyappa P, Braganza S, Chinnaiah S, *et al*. Retinopathy of prematurity in a rural neonatal intensive care unit in South India—a prospective study. Indian J pediatr. 2012;79:911-5.
16. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74:35-49.
17. Zin A, Florencio T, Fortes Filho JB, Nakanami CR, Gianini N, Graziano RM, *et al*. [Brazilian guidelines proposal for screening and treatment of retinopathy of prematurity (ROP)]. Arq Bras Oftalmol. 2007;70:875-83.
18. Guidelines for ROP Screening and Treatment in Latin American Countries. Available from: *https://www.paao.org/images/Downloads/.../2010_ROPGuidelines.pdf*. Accessed March 12, 2016.
19. Xu Y, Zhou X, Zhang Q, Ji X, Zhang Q, Zhu J, *et al*. Screening for retinopathy of prematurity in China: a neonatal units-based prospective study. Invest Ophthalmol Vis Sci. 2013;54:8229-36.
20. Chen Y, Li X. Characteristics of severe retinopathy of prematurity patients in China: a repeat of the first epidemic? Br J Ophthalmol. 2006;90:268-71.
21. Zepeda-Romero LC, Gilbert C. Limitations in ROP programs in 32 neonatal intensive care units in five states in Mexico. Biomed Res Int. 2015;2015:712624.
22. Patwardhan SD, Azad R, Gogia V, Chandra P, Gupta S. Prevailing clinical practices regarding screening for retinopathy of prematurity among pediatricians in India: a pilot survey. Indian J Ophthalmol. 2011;59:427-30.
23. Fierson WM, American Academy of Pediatrics Section on O, American Academy of O, American Association for Pediatric O, Strabismus, American Association of Certified O. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189-95.
24. Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee. Retinopathy of prematurity: An update on screening and management. Paediatr Child Health. 2016;21:101-4.
25. Wilkinson AR, Haines L, Head K, Fielder AR, Guideline Development Group of he Royal College of P, Child H *et al*. UK retinopathy of prematurity guideline. Eye (Lond). 2009;23:2137-9.
26. Chen Y, Xun D, Wang YC, Wang B, Geng SH, Chen H, *et al*. Incidence and risk actors of retinopathy of prematurity in two neonatal intensive care units in North and South China. Chin Med J (Engl). 2015;128:914-8.

27. Visser L, Singh R, Young M, Lewis H, McKerrow N. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP). S Afr Med J. 2013;103:116-25.

28. Zin AA, Moreira ME, Bunce C, Darlow BA, Gilbert CE. Retinopathy of prematurity in 7 neonatal units in Rio de Janeiro: screening criteria and workload implications. Pediatrics. 2010;126:e410-7.

WEB TABLE I SPECTRUM OF ROP AT AIIMS IN COMPARISON TO OTHER CENTERS

Characteristics	*Charan, et al. [10]*	*Gopal, et al. [12]*	*Vinekar, et al. [11]*	*Varughese, et al. [13]*	*Jalali, et al. [14]*	*Hungi, et al. [15]*	*Maheshwari, et al. [6]*	*Agarwal, et al. [7]*	*Kumar, et al. [8]*
Year	1993	1992-94	1993-2003	1999-2000	1999-2002	2008-2010	1992-1994	1999	2003-2008
Place	PGIMER, Chandigarh	Child Trust Hospital, Chennai	PGIMER, Chandigarh	St Stephen's hospital, Delhi	LV Prasad Eye Institute, Hyderabad	RL Jalappa Hospital, Karnataka	AIIMS	AIIMS	AIIMS
Total study population	165	50	138	79	1083	118	66	76	704
Birth weight/ GA of the population screened for ROP	BW = 1700 g	BW = 2000 g	BW >1250 g	BW <1500 g and GA < 34 wk.	BW < 2000 g GA < 36 wk.	BW = 2000 g and /or GA = 36 wk.	BW <1500 g GA> 35 wk	BW < 1500 g at birth and or GA < 35 wk.	BW =1500 g or GA =32 wk
Mean BW/ GA of infants with ROP	1285 g and 31 weeks	1355 g	Included only > 1250 g	NA	Included only ROP requiring laser/surgery or cicatricial disease. Mean GA 29.6/BW 1254 g	1555 g and 32 wk	All infants with ROP had GA =32 weeks and 3/4 had BW <1500 grams	1282 g and were 30.3 wk	1113 g and 29 weeks (infants with severe ROP)
Definition of severe ROP	= Stage III	Treatable ROP (CRYO ROP)	Treatable ROP (cryo-rop) + Stage 4 and 5	Treatable ROP (CRYO ROP)	Threshold ROP, pre threshold ROP Z one 1 stage 4A or more	ROP requiring laser (ET ROP)	Threshold ROP (CRYO ROP)	Stage III ROP	ROP requiring laser (ET ROP)
Incidence of any ROP	47.2%	38%	NA	51.8%	NA	41.5%	20%	32%	11.9 %
Incidence of severe ROP	12.8 %	16%	44.9%	6.3%	11%	10.2%	9%	21%; 8% required treatment	4.7%
Mode of Therapy	Not specified	80% Laser, Rest Cryo	Laser or Cryo	Cryotherapy	Laser/ Surgery	Laser	Cryotherapy	Cryo/ Laser	Laser
Comments	Among < 1000 g BW infants, 90% developed ROP	Absence of Zone I disease is probably related to the poor survival rate of very low-birth weight infants (<1000 gm).	In Indian scenario if western criteria for screening were applied; 17.7% of babies with threshold or worse ROP would be missed.	35% of small pre-term babies died in the nursery before they reached the age for screening.	13.3 % of babies with severe ROP would be missed if western screening criteria were to be applied. Criteria that combine GA < 34 weeks and BW < 1750 g would identify all babies in this study possibly missing only one	22.8% (29/118) of babies with any ROP would be missed if Western screening criteria are followed	Among < 1000g, 67% developed ROP. Blood transfusion and clinical sepsis were noted as risk factors for ROP		Incidence of any ROP and ROP requiring laser among ELBW neonates are 32.8% and 14.4 % respectively .