PERSPECTIVE

Can We Stop the Current Epidemic of Blindness From Retinopathy of Prematurity?

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Retinopathy of Prematurity (ROP) is a retinal vascular disease of the premature infant. There have been significant advances in the understanding of the pathogenesis, prevention, detection and treatment of severe ROP. In developed countries, all premature infants at risk for ROP are screened routinely based on national guidelines and treatment is prompt, resulting in good visual outcomes. Blindness from ROP is a rare event in these countries. However, there is an ongoing epidemic of ROP- induced blindness in India. The reasons for this epidemic of ROP blindness are many and include increasing survival of premature infants, lack of equipment such as oxygen-blenders and pulse oximeters that are necessary for safe use of supplemental oxygen in premature infants, lack of routine screening for ROP, lack of trained personnel for ROP screening, and lack of Ophthalmologists to promptly initiate treatment when infants develop severe ROP. All the identified causes can be resolved with a concerted national co-operative effort of Pediatricians, Neonatologists, Ophthalmologists, Indian Academy of Pediatrics, National Neonatology Forum, Indian Academy of Ophthalmologists, Government of India, and parents of premature infants. We feel that tt is possible to stop the current epidemic of preventable childhood blindness from ROP with concerted action by all stakeholders.

Keywords: *Neonate, Prevention, Retina*, *Strategy*.

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retinal vessels of premature infants. ROP screening of all 'at-risk' infants is the standard of care to detect ROP. Infants with threshold ROP need treatment within 48 hours to prevent ROP blindness. The World Health Organization has identified ROP as a priority area particularly in the middle income countries and urban areas of Asia. The number of infants blind from ROP in India will soon be equal to the rest of the world put together [1].

The Three Epidemics of ROP

Three epidemics of ROP have been described since the 1940s. During the first epidemic, blindness occurred in larger preterm babies in the western world due to unrestricted oxygen use. With restriction of oxygen use in the mid-50s, blindness from ROP decreased but there were increased rates of mortality and cerebral palsy [2].

The second epidemic of ROP occurred in advanced countries with increased survival of very preterm babies. ROP occurred in these very premature babies despite attempts at titration of oxygen. Currently patients who develop severe ROP in the Western world are extremely low birthweight and are identified by routine screening and treated in a timely fashion when indicated (mean birthweights of babies needing treatment range from 737 to 763 g) [3]. Few of them progress to blindness in the current era.

India and other middle-income countries are in the midst of a 'third ROP epidemic' that seems to be a combination of the first two epidemics as described above. With varying levels of care in the community, some larger institutes provide the highest levels of care, where only extremely premature infants develop ROP, whereas towns and rural areas, where neonatal care units are proliferating rapidly, even larger and more mature infants suffer from the disease [4,5]. It is projected that approximately 18,000 infants will go blind every year in India [1].

It is possible to substantially lower the incidence of ROP in India with better neonatal care. The experience from a newborn intensive care unit (NICU) in northern India shows that the incidence of ROP decreased from 47.2% [6] to 22.7% (P<0.05) over a 20-year period (unpublished data). This decline occurred despite a significantly lower median birthweight and gestational age, and increased survival of preterm infants in 2015

compared to a study from the same unit 20 years ago.

ROP in India

In India, relatively large and mature babies with birthweight more than 1500g and gestational age more than 34 weeks have been reported to develop severe ROP. Shah, *et al*. [7] reported that the mean birthweight among babies with threshold or pre-threshold ROP was 1488g (range 760-2310g). In a semi-urban and rural ROP program, 6.3% of babies born with a birthweight of >2000g developed ROP requiring treatment [8]. In a rural cohort of 7106 babies, 20% of all those who required treatment would have missed screening if the US Guidelines were followed [5]. Vinekar, *et al*. [9] found that 45% of premature babies with birthweight >1250g with ROP had threshold or worse ROP [9]. Therefore, it appears that a sizeable part of the third epidemic that we are facing in India is actually a repeat of the first epidemic due to use of unregulated supplemental oxygen (100% oxygen).

POSSIBLE REASONS FOR THE ROP EPIDEMIC IN INDIA

High rate of prematurity in India: Thirteen percent of babies born live in India are preterm (defined as those babies born <37 weeks gestation) and the number is steadily increasing [10]. India has over 3.5 million premature babies born annually. Increased use of assisted reproductive technology, widespread increase in oxytocin and cesarean sections for non-medical reasons partially account for the high prematurity rate [11].

Better survival of premature babies: Survival rates amongst premature babies are improving. In a study on Special Newborn Care Units (SNCU) in the period 2006 to 2009, there was an annual decline in case fatality rate, with declines ranging from 4.6% to 48.1% [12]. Government of India has initiated the development of SNCUin all districts to provide newborn care. There is no formal provision for screening of premature infants for ROP and treatment, if indicated, in these SNCU. This may be become potential and fertile a source for ROP blindness. Survival rates among neonates born at 28-30 weeks of gestation have improved to 75% to 93% in hospitals with good infrastructure in India (from the public and private sector)[13].

Oxygen use without blenders: The guidelines from the National Neonatology Forum (NNF) for the accreditation of level II neonatal units mention "mandatory" and "essential" criteria. The "essential" (but not mandatory) criteria include availability of Ophthalmologist for ROP screening, air oxygen blenders for delivering graded oxygen in the delivery room and availability of pulse oximeter in the delivery room. Thus, a level II unit could potentially get accredited without having some of these facilities.[14]. The list of equipments prescribed for SNCU includes oxygen hoods and supply systems as essential pieces of equipment and oxygen concentrators as desirable, but there is no mention of air-oxygen blenders nor compressed air supply [15]. Infants are exposed to 100% oxygen when an indigenous underwater bubble CPAP device is used without blending. Treating preterm infants with 100% oxygen routinely, without adequate monitoring with pulse oximetry, can lead to ROP.

Not using pulse oximeters to monitor and guide use of supplemental oxygen: Many newborn units do not have an adequate number of fully functioning pulse oximeters. Shah, *et al*. [7] reported that most babies with severe ROP had received unmonitored supplemental 100% oxygen. The operational guidelines for SNCU do recommend pulse oximeter saturation targets in preterm infants and term infants [15]. However, there is no published data from India documenting the awareness and compliance of pediatricians to these oxygen saturation targets.

Lack of training among Pediatricians who resuscitate and treat premature infants: A cross-sectional questionnaire-based survey of healthcare personnel working in a district in Haryana showed that only 16% of medical personnel knew all the initial steps of resuscitation, and only 48% had complete knowledge of positive pressure ventilation [16]. While there is no data specifically regarding awareness of dangers of using 100% oxygen for resuscitation of premature infants, it would be reasonable to assume that the lack of awareness is widespread.

ROP-screening protocols are not widely followed: In a study from northern India, the authors evaluated 66 outborn infants who presented with stage 5 ROP [17]. The median age at presentation was 7 months (range up to 84 months); 86.4% had never been screened for ROP before. A situational analysis revealed that at least two of the NICU, where some of these babies were initially cared for, did not have a ROP screening program. In a telephonic survey, referral rates for ROP screening were found to be very low [18]. Only 58% pediatricians always referred eligible preterm babies for ROP screening; 8% referred only sometimes, and 34% never referred. The commonest reason provided for non-referral was non-availability of trained ophthalmologists.

POSSIBLE SOLUTIONS

Increase the availability of compressed air supply and air-oxygen blenders; and train doctors and nurses: There are two types of air-oxygen blenders available in India, electronic and mechanical. Blenders have separate inlets

for compressed gas supply of air and oxygen. The device blends air and oxygen to provide the desired FiO_2 and the blended gas can be delivered at a desired flow rate. Electronic blenders use a solenoid for apportioning the amount of compressed air and oxygen to be mixed whereas mechanical blenders use a diaphragm. The electronic oxygen blenders cost approximately Rs. 100,000 to 150,000 per piece and the mechanical blenders cost approximately Rs 25,000 to 50,000. Air-oxygen blenders should ideally meet the following specifications: work with gas supply pressures ranging from 30-75 PSI; deliver oxygen concentration in the range 21-100%; the accuracy of the delivered FiO_2 should be ± 3% throughout the range of FiO_2; should have provision to deliver blended gas at high flow rate (1-15 L/min) and low flow rate (0.5-3 L/min); should be usable in premature babies weighing less than 2 kg and should be both wall mountable and pole mountable.

All newborn units (including SNCU) must be equipped with compressed medical air and sufficient air-oxygen blenders. We suggest that the SNCU guidelines include these facilities. The Neonatal resuscitation program (NRP) provides an opportunity to train and sensitize doctors and nurses regarding the danger of treating infants with 100% oxygen. The list of equipment required for NRP training must include an oxygen blender and the program must include the skills for setting up a blender and adjusting the oxygen concentration during resuscitation. The NNF accreditation guidelines for Level II units must move the need for air-oxygen blenders and pulse oximeters in the delivery room from the list of "essential" items to the list of "mandatory" items so that these become compulsory for accreditation.

Disseminate knowledge about oxygen saturation targets: The optimum oxygen target range recommended, as per current consensus seems to be that in preterm infants less than 28 weeks gestation, is 90-95%. Although, there are no definite guidelines for infants born beyond 28 weeks, oxygen saturation target range of 90 to 95% would generally be considered safe in this group as well. A higher nurse: patient ratio in Indian neonatal units would contribute to better compliance with the target oxygen saturation range.

Improve ROP screening and treatment: Wall charts must be prepared regarding which premature babies need screening and when for ROP. These charts should be posted in all nurseries (SNCU, NICU), nurseries and labour rooms all over the country to create awareness about timely screening of ROP. The ROP guidelines currently being prepared by the Government of India has mandated that babies born less than or equal to 2000 grams be screened, beginning not later than 30 days after birth. Details on the mandatory training required to screen or treat the disease have been laid down.

With the lack of ROP specialists across the nation and with the large load of 'at-risk'infants in the rural areas, a tele-ROP approach appears to be an excellent option [19]. The Karnataka Internet Assisted Diagnosis of ROP (*KIDROP.org*) was the country's first attempt in this regard [8]. Initiated in 2008, KIDROP employs trained technicians who travel within geographically defined zones covering several NICU each day. They use a portable, wide-field digital retinal camera (Retcam Shuttle, Clarity MSI, CA, USA). They grade and report these images based on a decision support algorithm; and the images are also uploaded on a server for the remote specialist to report from his/her smart phone within 90 minutes [5,20]. The National Task Force for ROP is currently using the KIDROP experience to expand to other states. Five other states have already implemented similar programs.

Maintain a nation-wide database of all babies who are treated and those diagnosed with ROP blindness: The exact number of infants who develop blindness from ROP each year in India is not known. At this time, the number of such infants is an estimate. The current SNCU guidelines do not include incidence of ROP in the dashboard indicators or in the prescribed reporting format. If one is to establish a surveillance system for ROP in India, the incidence of ROP must be included as a dashboard indicator by SNCU. The most pragmatic approach to identify, tag and follow-up babies with ROP would be to integrate the surveillance system with the SNCU database. If ROP fields and follow-up are integrated, text messages to the ophthalmologist who needs to follow-up these babies, a line listing at the taluk and district level, and a closely monitored surveillance system can be operational very soon. The national task force for ROP has already made significant progress in this regard.

The Rashtriya Bal Swasthya Karyakram (RBSK), a child health screening and earlyintervention program since 2013, under the National Health Mission, includes ROP as one of the defects at birth that will be detected at 0-6 weeks of age . In 2013, the UK-based Queen Elizabeth Diamond Jubilee Trust's Retinopathy of Prematurity Initiative convened a summit meeting in Delhi to prevent the development of ROP among premature babies in India. A five-year national plan was formulated to tackle the epidemic of ROP. The National Task Force for ROP is promoting neonatal care guidelines within India and to raise awareness about ROP.

Introduce newer technology for diagnosis: Newer, low cost, wide-field imaging cameras for ROP screening are being developed. These may be available in near future. These cameras would have the potential for ROP screening by non-ophthalmologists. With the uptake of this imaging technology, one expects there will be a paradigm shift in the ROP screening program from the standard 'ophthalmologist-led' model to a 'neonatologist' or 'non-physician-led' model with links to accredited ROP-trained specialists would be harnessed when the infant needs treatment Relying on non-objective methods of indirect ophthalmoscopy, perfor-med by inadequately trained ophthalmologists leads to lack of documentation and could invite medico-legal liability.

Educating parents regarding ROP: Physicians taking care of premature infants should inform the parents regarding the risk of ROP, timing of ROP screening, the specialist involved in screening (in the birth hospital or elsewhere) and the need for urgent treatment for infants who progress to threshold ROP. This parental education should take place before any premature infant is discharged. If the birth hospital does not have a ROP-trained specialist, the infant should be referred to such a specialist and parents should understand the importance of the referral. Parental education (verbal and/or written) is critical to decrease the risk of ROP blindness in any given infant.

Conduct research to understand the epidemiology of prematurity and translational research to minimise the known risk factors of ROP: There is currently very little information regarding the epidemiology and risk factors of prematurity in India. The Department of Biotechnology (DBT), Government of India has embarked upon a major national program to elucidate the co-relates, causes and predictors of preterm births in India under its grand challenges program. Data from this program is expected to go a long way towards understanding and reducing the burden of premature births.

Studies from India have repeatedly shown sepsis, blood transfusions and double volume exchange transfusions for hyperbilirubinaemia to be important risk factors, particularly so in bigger neonates. Academic bodies in India must actively disseminate guidelines for hand hygiene measures, aseptic routines to reduce the incidence of sepsis, guidelines for packed red cell transfusions and exchange transfusions to restrict exposure to blood products and guidelines for effective maintenance of phototherapy devices. There is an urgent need for translational research in India to find ways and means for implementing existing knowledge for the reduction of risk factors of ROP.

CONCLUSION

The possible actions that could be used to decrease ROP blindness would be to *a*) develop national guidelines and research to decrease preterm births; *b*) making available oxygen blenders and pulse oximeters so that preterm infants' are exposed to optimal supplemental oxygen; *c*) mandated ROP screening of all preterm infants and timely treatment of infants' with threshold ROP, *d*) adequate training (National, state-wide, regional) of all doctors, who take care of preterm infants, regarding use of supplemental oxygen, oxygen blenders, pulse oximeters and prompt referral for ROP check, and *e*) promoting new imaging technology that allows point of care screening of at-risk infants.

India is in the midst of a tragic epidemic of ROP blindness that is not only occurring in very premature babies but also in heavier and more mature babies. The authors strongly believe that this tragedy needs immediate action as outlined above. One more blind child, from a preventable cause such as ROP, is one too many.

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