Curr Pediatr Res 2015; 19 (1 & 2): 37-43 *ISSN 0971-9032*
www.currentpediatrics.com

Analysis of Retinal Imaging System for Premature infants: A review

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Abstract

In this paper, we have reviewed the prominent disease in premature infants, Retinopathy of Prematurity (ROP) which has become the leading cause of blindness in children. We have also reviewed the existing retinal imaging systems and their screening procedures, particularly for premature infants. The classification of Retinopathy of Prematurity (ROP) and its status, specifically in a developing country like India, has been discussed. The profile of the ROP babies in developing countries is very different from that in the developed countries. The screening cut off for the babies and the risk factors are also peculiar in developing countries. Current ROP imaging modalities have been analyzed and their limitations have been studied. Initially, ROP screening was done by Binocular Indirect Ophthalmoscopy (BIO), which is considered as the gold standard for ROP screening. Later, digital screening for ROP was started, with the advent of RetCam and other digital cameras. Further improvements to these systems have been identified here that would improve the field-of-view, image acquisition speed, image quality and various other factors.

Keywords: Childhood blindness, Retinopathy of Prematurity, Binocular Indirect Ophthalmoscopy, RetCam.

Accepted July 13 2015

Introduction

Childhood blindness refers to a group of diseases and conditions, which, if not treated at the right time, can lead to permanent vision loss in children at early stages of their life. Control of blindness is one of the main priorities set for achieving the goals of Vision 2020: the right to sight. This is a programme launched by World Health Organization (WHO) for the elimination of avoidable vision impairment [1, 2]. It has been reported that 4-5% of all blindness in the world is due to childhood blindness [3]. In India, children below the age of 16 years, alone account for 40% of the entire population [1]. Studies conducted to estimate the prevalence of childhood blindness in India, reported that about 320,000 children are visually impaired [3]. Other studies also reported that the majority of these children are likely to be in the poor segment of the population [2].

Major causes of visual impairment in children are Vitamin A deficiency, corneal scarring, congenital cataract, Retinopathy of Prematurity (ROP) and congenital glaucoma. These diseases, if addressed in their early stages, can save a child's vision for the rest of its life [3]. Among the various eye diseases addressed above, ROP is a prevalent disease in the premature infants and is a leading cause of impairment in children in the developed as well as developing countries [4-6]. In India, ROP was first reported anecdotally in 1992 and prospectively in 1995 [7]. Since then, in the past two decades, the major cause for blindness in children is ROP, for the simple reason that the number of infants being born premature has increased tremendously. In the developing countries, including India, the incidence of ROP has been increasing, not only due to high birth rates, but also due to the increase in survival of low and very low birth weight infants. This is due to the development of neonatal intensive care units, hence improved neonatal care, and these incidences are expected to increase exponentially in the near future due to the aforementioned reasons [8-10].

Classification of Retinopathy of Prematurity

ROP was first described by Terry in 1942 [8]. The basic reason for the development of this disease is, in preterm infants, the retinal development is incomplete; as such development takes place during the course of gestation. The blood vessels develop from the optic nerve anteriorly to the ora serrata. The extent of immaturity of the retina depends on the degree of prematurity at birth [11]. ROP is associated with abnormal vascular development of the retina, since the development takes place after the post-menstrual period in these infants [6,8]. The risk factor,

during the initial years, was found to be high levels of oxygen supplementation given to the infants with the interest of saving their lives [8,12,13]. However, the detection was made only when the disease entered its last stage. Screening for ROP was possible only after the advent of Binocular Indirect Ophthalmoscopy (BIO) in 1970s [14]. This was a major advancement which helped early detection and diagnosis of ROP. The risk factors, now, include the low birth weight (less than 1500 grams) and the gestational age (less than 32 weeks) of the premature infants [8, 12].

An international classification of ROP in 1984 presented a further significant advancement in this field [12,14,15]. It was later expanded in 1987 to provide the medical community caring for the infants at risk of ROP with a detailed description of the disease and present an optimized management, care and treatment of this vision threatening disease [7]. Therefore, according to the Revised International Classification of Retinopathy of Prematurity, the disease can be categorized with respect to the location, extent, stages, aggressive posterior ROP, plus and pre-plus disease. The location of the disease in the antero-posterior part of the eye is described with the help of three concentric zones. Zones are the areas which describe retinal vascularization. Zone I shows the vascularization in the circular area centered on the optic nerve, whose radius is twice the distance from the center of the optic nerve to the center of the macula. Zone II extends beyond zone I, with radius defined as the distance from the optic nerve to the nasal ora serrata, and extends to the equator on the temporal side. Zone III is the residual crescent of the retina anterior to zone II. ROP should be considered to be in zone II until the vascularization has reached ora serrata. The extent of the disease is recorded in terms of clock hours, which are divided as sectors of 30 degrees each. The 3-o'clock position is towards the nasal in the right eye and temporal in the left eye. Similarly, the 9-o'clock position is to the temporal in the right eye and nasal in the left eye [15].

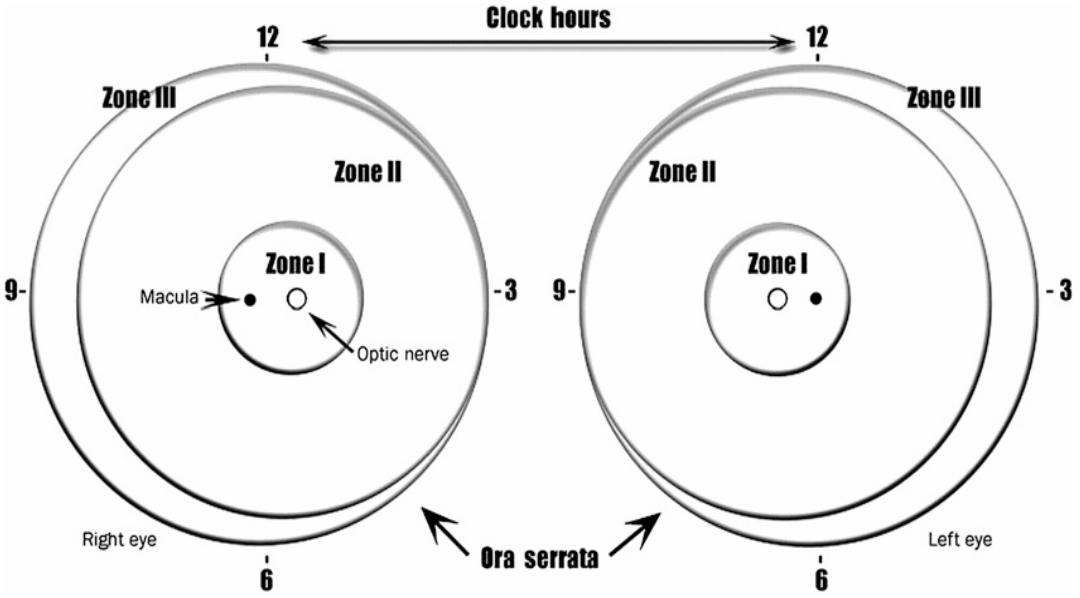


Figure 1. *Scheme of retina of right eye and left eye showing the classification of ROP in terms of zone borders and clock hours which are used to describe the location and extent of ROP [11]*

Another important component of classification is based upon the five stages of the disease which describe the abnormal vascular response at the junction of the vascularized and avascularized retina. Stage 1 is the mild abnormal growth of the blood vessels, observed as a thin, tortuous, grey-white demarcation line, that runs approximately parallel to the ora serrata and divides the vascular retina posteriorly from the avascular retina anteriorly. There is abnormal branching of vessels up to the demarcation line which lies within the plane of the retina. This line forms a ridge, has a height and width, and extends above the plane of the retina. This stage is termed as stage 2. Stage 3 describes extraretinal fibrovascular proliferation which extends from the ridge into the vitreous. This gives a ragged appearance as the proliferation becomes more extensive. Stage 4 describes partial retinal detachment; stage 4a indicates extra foveal retinal detachment while stage 4b indicates macular detachment. This detachment is due to the contraction of the fibrous tissue and it continues to increase in height extending posteriorly as well as anteriorly. This progresses to stage 5, which describes total retinal detachment; the totally detached retina becomes a thickened mass posterior to the lens and is usually funnel shaped. Once stage 5 is reached, there is no cure of this disease which leads to the complete loss of vision in the infants [15].

The severity of the disease is also indicated by the presence of plus disease. Plus disease is defined as the posterior vessel dilation and tortuosity, which may later lead to increasing pre-retinal and vitreous hemorrhage, vitreous haze and poor pupillary dilation. The diagnosis of plus disease is made if sufficient vascular dilation and tortuosity are present in at least two quadrants of the eye. The vascular abnormalities observed in the eye before the severity reaches to plus disease is termed as the pre-plus disease. It is defined as the vascular abnormalities present which are insufficient for the diagnosis of plus disease but show more arterial tortuosity and venous dilation than observed in normal eyes [15].

The threshold for the treatment of the disease is defined by the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) as at least five continuous or eight cumulative clock hours of stage 3 ROP in zone I or II, associated with plus disease [4,16,17]. It is observed that many premature infants develop some degree of ROP, although in the majority of them, it regresses spontaneously without treatment by the process of involution or evolution from a vasoproliferative phase to a fibrotic phase [4, 15]. However, in certain cases, it increases to pre-threshold and threshold levels; where in diagnosis through retinal screening becomes mandatory. Screening of the infants provides a better prognosis and increases the survival rate of the infants. The Early Treatment for Retinopathy of Prematurity (ETROP) study also confirmed the importance of retinal screening [4]. In the Multicenter Trial of Cryotherapy for ROP, early detection and treatment of ROP have shown to decrease the incidence of severe visual loss and adverse outcomes in premature infants [19, 20]. The current ROP screening criteria given by the American Academy of Ophthalmology, the American Academics of Pediatrics and the American Association of Pediatric Ophthalmology and Strabismus is to screen the infants with birth weights under 1500 grams or gestational age of 30 weeks or less and selected infants

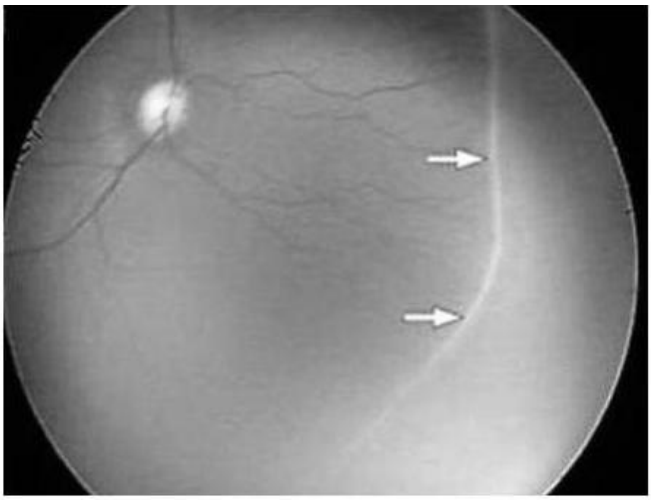


Figure 2(a). *Stage 1-the demarcation line*

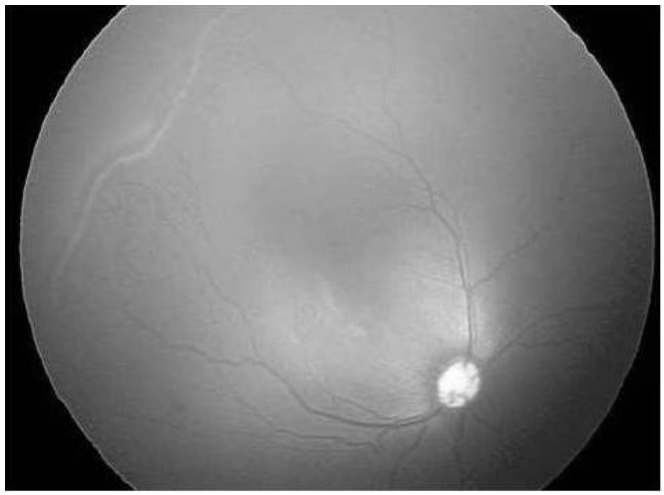
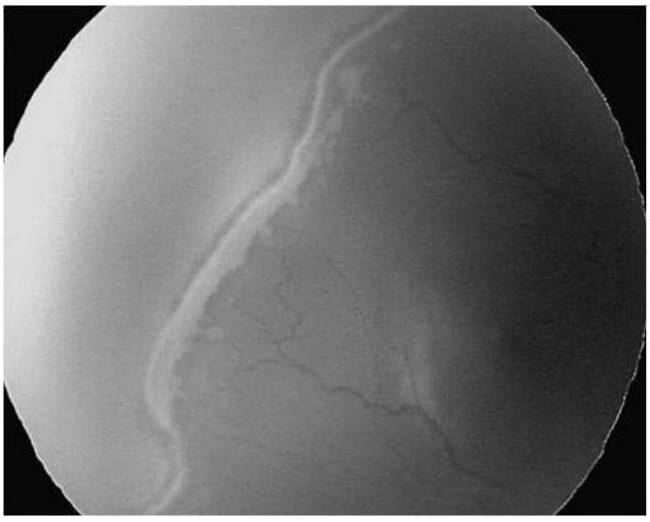
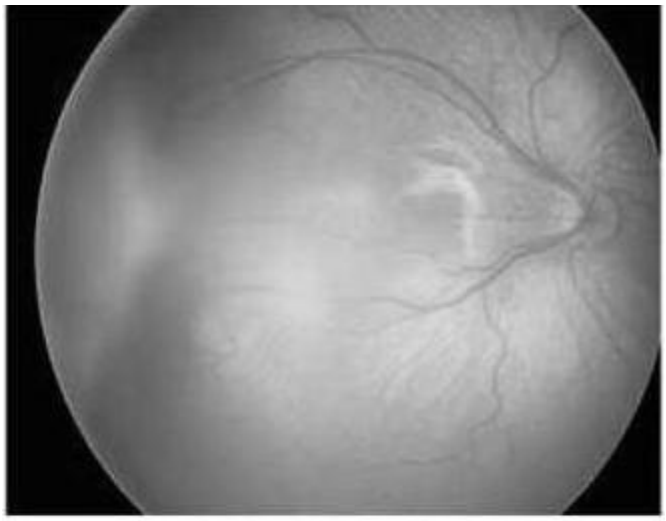


Figure 2(b). *Stage 2 -the ridge[15]*





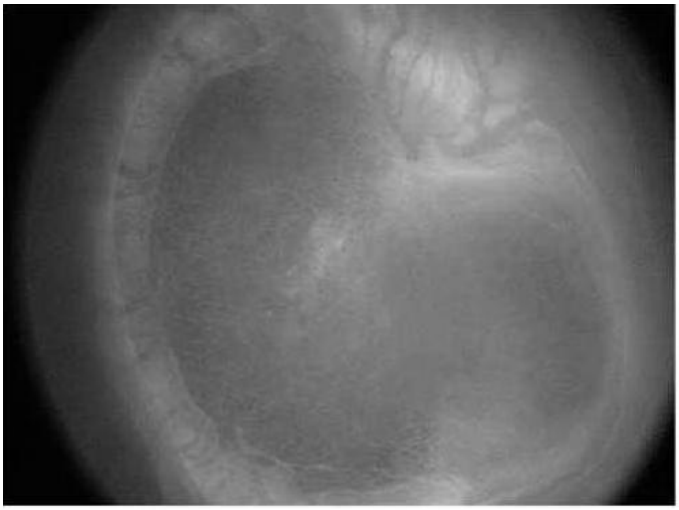


Figure 4(a). *Stage 5- total retinal detachment of the retina*

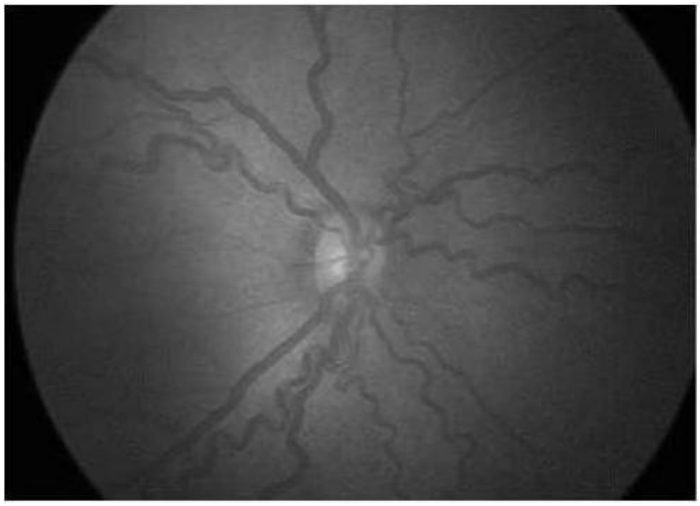


Figure 4(b). *Plus disease-vessel dilation and tortuosity [15]*

with a birth weight between 1500 grams and 2000 grams or a gestational age greater than 30 weeks with an unstable clinical course who are considered at high risk by their neonatologists [4,18].

The treatment is given either by cryotherapy or laser photocoagulation, for ablation of the peripheral retina [12, 16, 17]. The treatment criteria for severe disease, using the above mentioned procedures, have been established through CRYO-ROP and Early Treatment for Retinopathy of Prematurity (ETROP) trials [18].

ROP in India

It is well recognized that the profile of the ROP babies in developing countries is very different from that in the developed countries. In developing countries, relatively older and heavier babies are likely to develop severe ROP, thus increasing the burden for the number of babies that need to be screened [5]. Apart from the screening cut off, the risk factors are also peculiar in developing countries. In India, the risk factors also include packed cell and double volume exchange transfusions, anemia, outborn status, thrombocytopenia etc., as reported by Bhavana et al [7]. They performed the first prospective study from India which reports the spectrum and outcome of ROP in a rural environment. The study also identified that the nurseries in urban areas have shown improving trend of neonatal care with improvement in the babies suffering from severe ROP, whereas in the rural areas, the babies are at a greater risk to develop severe ROP. It is reported that the babies outside the American screening cut off are at risks of developing severe forms of ROP [1]. Thus, if the western guidelines are used for screening in the rural parts of India, we might risk missing a significant proportion of infants who may require treatment. Thus, the screening cut off for Indian babies has been suggested to be kept as 1,750 grams. Apart from the screening cut off, the risk factors are also peculiar to Indian infants. They include packed cell and double volume exchange transfusions, anemia,

outborn status, thrombocytopenia etc. Presently, most of the information we have about the incidence and profile of these ROP babies in India have come out of studies conducted in tertiary care centers in big cities.

Although the number of blind children is large and the incidence of ROP is increasing drastically, yet pediatric ophthalmology is not a well-established, distinct subspecialty in India, and is still in its budding stages. Moreover, the available centers are not homogenously distributed across the country; a complete lack of services in the North and East whilst South and West were observed to show better ratios [1]. However, with the improvement in the neonatal care services, many level II nurseries have mushroomed across semi urban and rural parts of India, therefore, many premature babies are surviving in these areas. Still, there is paucity of ROP care givers as most of the vitreo-retinal surgeons and pediatric ophthalmologists practice in the bigger cities, hence, there is a growing scarcity in the number of ophthalmologists required for diagnosing ROP in the semi-urban and rural areas [18].

Current ROP screening strategies

Even though ROP was identified in 1942, screening for ROP was possible only after the advent of Binocular Indirect Ophthalmoscopy (BIO) in 1970s [14]. Since then, BIO is recognized as the gold standard for ROP screening [4]. The examination is performed by an ophthalmologist, using an indirect ophthalmoscope and a hand held 28 or 30 dioptre convex lens. The infant's eye lids are prise opened using eye speculum and a low intensity of illumination is used to illuminate the interior of the eye. In order to visualize the required areas of the retina, the oculocephalic reflex is used. If needed, scleral identor is also used in order to rotate the eye ball during examination

[13]. This examination should be performed by an ophthalmologist who has sufficient experience and knowledge in the examination of infants for ROP. Advantages of BIO include complete documentation of ROP and usually better visualization of the fundus by the ophthalmologist [19].

A common device used for the diagnostic purposes is RetCam 120(Massie Laboratories, Inc., Pleasanton, CA, USA), which is a hand held digital retinal camera, frequently used for ophthalmic examination. The screening of ROP using this digital imaging device has proved as a potential alternative to BIO. It provides high-resolution images using a 3-CCD (Charge Coupling Device) digital camera coupled to a family of lens units, which includes a 130-degree unit designed for screening of ROP cases, a standard 120-degree unit, a high-magnification 30-degree unit, a high-contrast 80-degree unit (used for adults), and the flat-field portrait lens which can be used for external photographs. The images obtained are 640 X 480 pixels, approximately 900 kB in size, with a resolution of 72 pixels per inch and a realistic color match. Focus and illumination adjustments can be performed manually, either on the base unit or with a foot pedal [20].

The procedure involves lubricating the eye with an ophthalmic lubricant and gently placing the 130-degree Field of View (FOV) contact lens of the camera on the eye [4]. Five to ten images are captured and are digitally stored [19]. These images can be diagnosed by the ophthalmologists at a later, convenient time. This device provides an ease of use, with excellent reproducible images when compared to BIO [4]. Moreover, it can be performed by a technician or a trained nurse, with more flexibility in the scheduling of the diagnosis [19]. For obtaining optimal image quality of the images, wide pupillary dilation, a clear crystalline lens, and light to medium fundus pigmentation would be required [20].

Figure 5. *Image showing RetCam in non-contact mode to visualize the anterior segment [6]*

Limitations of the existing techniques

The BIO technique is the accepted strategy for examination of ROP. However, it has a number of limitations. BIO is a time consuming procedure; it also depends on the availability and time constraints of the ophthalmologist [19,21]. Thus, the ophthalmologists are confronted with the challenge of providing the service to more infants with limited resources, in a climate of high liability, when there is already a growing shortage of trained ophthalmologists [21]. RetCam overcomes some of the limitations, yet it also proves to be disadvantageous, if it is to be used in a developing country like India. The first techno economical factor is the initial cost of the device, which is not affordable for mass screening in the developing countries. Despite the excellent reproducible images, the image quality is poor and limits the detection of ROP [19]. This could be due to the difficulty in imaging

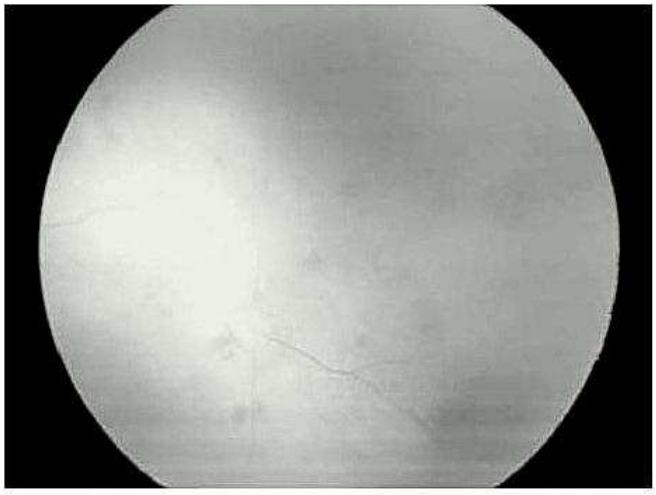


Figure 6. *RetCam fundus photograph taken 70 minutes after the initial examination. There are multiple flame-shaped, 'dot' or 'blot' retinal haemorrhages that indicate bleeding at different depths within the retina [23]*

the small eyes of the infants with small palpebral fissures. It is also observed that RetCam has insufficient sensitivity to image the peripheral retina of 32-34 weeks infants [21]. However, there are other factors that reduce image quality. Extreme prematurity with narrow palpebral fissures prevent good corneal contact with the lens nosepiece. Media opacity from corneal clouding, pseudophakia, or congenital cataracts can reduce the quality of the images. Poor mydriasis results in a dark, round or ring-shaped artifact. Moreover, dark pigmentation in the choroidal region can impair visualization of retinal vascular details [20].

Apart from these, some of the limitations are common to both BIO and RetCam. ROP screening appears to be painful and uncomfortable for the infants due to the nature of examination, which involves insertion of speculum, use of identor (in case of BIO) and a considerable amount of handling. The stress responses recorded during the procedure were the infants' crying patterns, neurobehavioral activity and physiological responses [14]. Infants have

also been shown to experience changes in the levels of oxygen saturation, blood pressure, pulse rate and gastric mobility due to the administration of eye drops or lubricant [21, 22]. Retinal hemorrhages have also been observed in some cases, following RetCam screening, emphasizing the fragility of the infants [23]. Another limitation is that the interpretation of ROP from BIO or RetCam requires expert knowledge about ROP, for which we need trained ophthalmologists [11]. This problem further increases in rural or semi urban areas where the ophthalmologists may or may not be readily available [18].

Conclusion

It can be seen that ROP is a potentially blinding disease occurring in premature infants, affecting the postnatal maturation of the retinal blood vessels. In some cases, it regresses on its own while in others it progresses and needs immediate and weekly screening of the retina. Treatment is given to the infants who have reached the threshold level of the disease, followed by screening till the retinal development is complete. It is observed that the existing imaging procedures are tedious and troublesome. From our findings, the lens used in digital imaging does not capture the peripheral retina, hence the handheld imager needs to be rotated over the cornea to focus and image the peripheral parts of the retina. This also shows that the existing device is not ergonomically suited for mass screening. The current system is non-portable and cannot be easily carried from one place to another. The images so obtained from the infants' eyes, need to be interpreted by the ophthalmologists, who might not be on site or available at the time of the screening. The interpretation is also difficult in some cases, due to the poor image quality.

Perspective

Pediatric ophthalmology is becoming increasingly recognized and the need of the day is to develop a pediatric eye care team and augment their skills. It has been observed that there is inadequacy of the number of trained pediatric teams and available pediatric eye centers in India and hence these numbers should increase for the delivery of effective eye care. Among the diseases affecting small children, ROP is a well-recognized disease in the premature infants and needs to be addressed at its early stages to prevent the infants from turning blind. The present screening techniques include BIO and RetCam. Various advantages of RetCam were observed in comparison to BIO; the main advantage being the provision of wide field digital imaging. However, there are limitations to this device as well. Apart from the device limitations, it is also observed that ROP screening proves distressing to the infants as well.

A device which has wider field of view to capture the peripheral retina, portable and ergonomically suitable can be the best possible solution. It should be capable of high quality image acquisition, image processing, storage and transmission. Furthermore, it should also consider the economic factors and can be made as a cost effective device. Last but not the least, a semi-automated device to detect the stages and plus disease will be of a great help to the doctors and ophthalmologists.

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