REVIEW ARTICLE

Ocular Morbidity Associated With Retinopathy of Prematurity in Treated and Untreated Eyes: A Review of the Literature and Data From a Tertiary Eye-care Center in Southern India

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Retinopathy of prematurity (ROP) is an emerging cause of childhood blindness in low- and middle-income countries. We review the magnitude, causes, prevention and treatment of visual impairment caused by ROP over a time span. A review of literature on short and long term structural and functional outcomes of ROP was conducted through PubMed search primarily focusing on studies published during the last decade. Additionally, we have shared data from our institute located in Southern India. Visual Impairment in ROP-treated children ranged from 4.1% to 30% in various settings, attributable mainly to refractive errors, amblyopia, strabismus and perinatal neurological events followed by structural changes like macular scarring and retinal detachment. We conclude that towards an early detection and a proper management of all the above mentioned conditions, these children need to be followed-up for a long time by a committed pediatric ophthalmologist at a specifically scheduled interval. The overall success depends upon the strength of the networking system between parents/neonatologists/pediatricians/pediatric ophthalmologist and a retina specialist.

Keywords: *Blindness, Outcome, Prematurity, Visual impairment.*

In the past decade, there have been major advances in the management of ROP; still, eyes with the sight threatening stages of the disease can develop a range of ocular morbidities many of which are visually impairing even if treatment led to resolution of the ROP [1]. These include refractive errors, *i.e.* myopia (short-sightedness), hypermetropia (long-sightedness) astigmatism (distorted sight), anisometropia (different refractive errors in the two eyes), and strabismus (squint). All these conditions, if not detected and adequately managed in time, can lead to amblyopia ("lazy" eye). Anterior segment conditions (*e.g.*, glaucoma and cataract) can also occur. There may also be residual changes in the retina such as displacement of the macula from scarring in the peripheral retina (macular dragging), retinal breaks, macular degeneration, and late onset retinal detachment. Laser treatment can sometimes lead to peripheral visual field defects.

Retinopathy of prematurity, which previously was an important cause of blindness in the developed world, is now emerging as an important cause of blindness and visual impairment in low- and middle-income countries [2,3]. It is important that pediatricians, neonatologists and nurses who care for preterm infants, understand the multiple causes of visual impairment which can affect children born preterm and the role they can play in maximising normal visual development.

OUTCOMES OF CLINICAL TRIALS FOR ROP

The most informative data on the structural and functional outcomes of ROP (treated and untreated) come from the following clinical trials: Early Treatment for ROP (ETROP) [4]; Cryotherapy for ROP (CRYO-ROP) [5] and Bevacizumab Eliminates the Angiogenic Threat from ROP (BEAT- ROP) [6], the latter being the only trial to use an anti-VEGF agent. The CRYO-ROP trial, which used peripheral retinal cryotherapy, compared treatment of threshold ROP with no treatment. ETROP was designed to determine whether earlier peripheral laser treatment would give better functional and structural outcomes than laser treatment at threshold ROP. The BEAT-ROP trial compared laser with intravitreal injection of the anti-vascular endothelial growth factor (VEGF) agent, Bevacizumab (IVB). All these trials were undertaken in the United States, and all recruited infants with a birthweight of <1500g (BEAT-ROP). Infants recruited to these trials have been followed up over time, with high rates of attendance. These studies, therefore, provide the most reliable data on the longterm outcome of *a*) untreated ROP (CRYO-ROP), *b*) threshold ROP treated by cryotherapy (CRYO-ROP) or laser (ET-ROP), *c*) type 1 prethreshold ROP treated by laser, and *d*) a comparison of laser and Bevacizumab treatment (***Web Table* I**). These clinical trials

demonstrate that visual impairment and refractive errors of several types frequently occur after treatment for ROP, and high degrees of refractive error can occur, particularly myopia (***Web Table* I**).

The population of infants developing sight threatening ROP (*i.e.* where treatment is indicated) in low/ middle income countries (LMIC); however, differs from that in high income settings, with more mature infants being affected [7]. Among the 46 babies treated for ROP at Aravind Eye Care System (AECS), a tertiary-eye care institution in Madurai, India, in the year 2015, 8 (17%) had gestational age ranging from 33 to 36 weeks and 11 (24%) had birthweights more than 1500g. Aggressive Posterior ROP (APROP) was diagnosed 17.4% of eyes and 10.5% presented with stage 4 or 5 ROP. Long-term follow-up data from the trials outlined above, may not, therefore, be applicable to infants treated in LMIC settings, where eyes as well as infants can be larger. The purpose of this study was to review the literature on ocular morbidity and visual outcome in ROP-treated eyes focussing on studies published worldwide over the last decade, and to report follow up data from AECS.

VISUAL IMPAIRMENT DUE TO ROP

In 2010, there were estimated to be almost 15 million preterm births globally, 2.3 million (15.3%) of whom were born before 32 weeks gestational age with the remainder born at >32-36 weeks [8]. Among those born before 32 weeks, 157,800 survivors (15.8%) were estimated to develop ROP, 30,300 of whom became blind (presenting visual acuity of less than 3/0 in the better seeing eye) or visually impaired (presenting visual acuity of less than 6/18 to 3/60 in the better seeing eye). The figures were 26,900 and 2,000, respectively among those born after 32 weeks gestational age [3] Overall, 15-16% of premature births were projected to require screening or treatment for ROP and 3-4% would require visual rehabilitation, education and family support. In addition, 55% of visually impaired infants were estimated to have neuro-developmental comorbidity.

Studies from a range of settings on the long-term outcome following laser treatment for ROP reveal that 4.1-30% of eyes / infants become visually impaired (***Web Tables* II** and **III**). However, in only 1-25% of cases was visual loss due to unfavorable outcomes in relation to the retina, such as retinal detachment or macular scarring or dragging secondary to ROP. The main causes of visual loss (75-99%), were refractive errors, amblyopia, strabismus and perinatal neurological events.

In 2015, 66 children (122 eyes) treated for ROP at the AECS were reviewed at ages 2 to 9 years. All had been treated with laser or intra-vitreal Bevacizumab (unpublished data, Vijayalakshmi, *et al*., **Web Table II and III**). At presentation, 6 eyes had APROP and 13 had stage 4 or 5 ROP. Thirty-eight eyes (31.7%) were visually impaired: moderate in 16 (13.3%) and severe in 8 (7.5%), and 14 (10.8%) eyes were blind. The reasons for visual impairment were structural abnormalities (*e.g.*, retinal detachment, macular dragging, optic atrophy) in 17 (44.7%) eyes, high myopia in 4 (10.5%), amblyopia in 2 (5.3%) and cortical visual impairment in 15 (39.5%). Twenty of the 24 children who were visually impaired (83.3%) showed some degree of developmental delay.

It is, therefore, imperative that infants and children who have been treated for ROP be followed up adequately and periodically by a pediatric ophthalmologist during the crucial period of ocular growth and visual development i.e. during the first 5-6 years of life.

Refractive Errors: The proportion of eyes treated for ROP which develop refractive errors ranges from 29.7% in extremely preterm infants in Sweden [9] to 67.2% in our series in India (***Web Tables* I** and **II**).

Myopia: Myopia in premature babies can be associated with prematurity without ROP, spontaneously regressed ROP and treatment for ROP.

The incidence of myopia following laser treatment for ROP has been reported to range from 50-94% (means -2.11 to -5.11 D) in children aged >7years and 26-80% (means –4.71 to -6.69D) in those aged 1-5 years with 16-35% of children had myopia greater than -4D (***Web Tables* I** and **II**). In the ETROP study, approximately two-thirds of eyes treated for high-risk pre-threshold ROP were myopic at preschool and early school ages (***Web Table* I**). In our study, we had similar findings, as 67.2% of eyes treated for ROP had a refractive error, with myopia with or without astigmatism occurring in almost two-thirds (63%), and 14.3% having high myopia. Hypermetropia occurred in only 4.2%, including one aphakic eye.

Myopia in adults who were born at term is primarily due to an increase in length of the eye. However, the myopia of prematurity is due to changes at the front of the eye *i.e.*, a steeper cornea, shallower anterior chamber and thicker lens which change the optical properties of the eye [10]. Myopia of prematurity without ROP is of low magnitude and decreases with age, being inversely related to gestational age and birthweight. Myopia following spontaneously regressed ROP, is associated with the degree of prematurity as well as the severity of ROP [11-13] The degree of myopia tends to plateau by two-and-a half years of age.

On the other hand, eyes treated for threshold ROP with laser have a higher prevalence and greater severity of

myopia compared with eyes where ROP has regressed spontaneously, and the onset can be very early i.e. from 6 months to 3 years. The prevalence of myopia does not appear to increase thereafter, until at least 6 years of age [14]. The ETROP trial reported a higher rate of high myopia (>-5D) in eyes treated with high-risk prethreshold ROP in zone I than in those treated for zone II disease [14,15]. The prevalence of myopia was higher in eyes with retinal residua of ROP than in eyes with normal appearing posterior poles, highlighting the importance of follow-up eye examinations of infants treated for ROP.

Findings from the BEAT-ROP trial and other studies of intra-vitreal bevacizumab suggest that this treatment is associated with a lower risk and less severe myopia than laser treatment [16,17], which suggests that laser ablation of the peripheral retina may have a negative impact on the growth of the structures at the front of the eye.

Astigmatism: A high proportion of eyes develop astigmatism after laser treatment, ranging from 64.4% to 98% among threshold ROP treated children followed up for 6-9 years with 25-50% having >2D of astigmatism (***Web Table* I** and **II**). This is far higher than in term children [18]. By 3 years, nearly 43% of eyes treated for high-risk prethreshold ROP developed astigmatism of e"1.00D [19]. In all studies, the astigmatism in all age groups and all types of ROP treated was the same type *i.e*., with-the-rule (75°–105°) which may be explained by Yang's finding of steeper vertical corneal curvatures in laser-treated eyes compared with term controls. Our study revealed 58% of myopic astigmatism in ROP-treated eyes.

According to Holmstorm, *et al*. [20] by two-and-a half years of age, astigmatism is predictive of future refractive error in preterm infants [20]. It is important to detect and treat astigmatism early to prevent or reverse amblyopia.

Anisometropia: Anisometropia is commonly seen in laser-treated threshold ROP eyes, affecting 9.5%-46.7% by 6-9 years of age (***Web Table* II**). Our study revealed anisometropia in 7.1% of children, with higher degrees of myopia in eyes with more posterior and more severe retinopathy. Detection and treatment of anisometropia as early as 6 months is mandatory to avoid amblyopia and strabismus.

DETECTION AND TREATMENT OF REFRACTIVE ERRORS

Children with resolved ROP, particularly those who have been treated, need regular and frequent ophthalmologic care throughout childhood, including cycloplegic refraction and dilated retinal examination, to detect refractive errors as well as retinal abnormalities. These children need to be followed in centres with a pediatric ophthalmologist, and optometrist skilled in conducting refraction in young children.

Infants with regressed ROP should undergo cycloplegic retinoscopy at 6 months of age and every 4 months until they reach the age of two years. Further, 6-monthly reviews should be scheduled until the refractive error stabilizes. The following regime is recommended for infants less than 12 months of age for cycloplegia: cyclopentolate 0.5 % with phenylephrine 2.5% eye drops instilled twice 10 minutes apart, to avoid the systemic complications of higher strength cyclopentolate. In children aged 1-5 years, 1% cyclopentolate eye drops (instilled as above) or 1% atropine eye ointment once a day.

Anisometropia is initially treated with spectacles alone for the first 8 weeks. A contact lens is an option for high anisometropia. Children with amblyopia should be reviewed after 8 weeks of spectacle wear. If amblyopia persists, occlusion therapy is instituted.

Strabismus and Amblyopia

In strabismus, one eye may be deviated inwards *i.e.*, towards the nose (esotropia) or outwards (exotropia). In follow-up studies of infants with ROP, most report esotropia and exotropia with equal frequency, which differs from term children where esotropia is more common. Strabismus can be detected in infants and children by drawing their attention to a torch penlight, and observing the location of the light reflex on the cornea in relation to the pupil. If the reflex is not centred on the pupil, then this suggests strabismus and the child should be referred. If an eye appears to be deviating, it is important to rule out changes in the retina, such as macular dragging, which may mean that the visual axes are aligned even if the eyes may not appear to be ("pseudo-strabismus").

The incidence of strabismus is much higher in preterm than term infants, affecting approximately 14.7% of cases [21]. The greater the severity of ROP the higher the incidence of strabismus at 6 months of age [22]. In the ETROP trial, 42.2% of laser-treated eyes developed strabismus [21], being reported in 5.6%-54.4% of children in other studies (***Web Tables* I** and **II**). However, studies reveal that many infants with strabismus at 6 months no longer had strabismus 3 months later. Strabismus in ROP treated eyes is strongly associated with prematurity, poor vision, amblyopia and periventricular leucomalacia (PVL) [23]. In our study, 30/122 children (25%) developed strabismus with esotropia and exotropia being almost equal.

Treatment of persistent strabismus entails correction of any refractive error, occlusion of the better seeing eye, if

amblyopia is present, and finally, surgical correction to realign the eyes. Vanderveen, *et al*. [22] suggest that because of the variability in alignment, conservative management of strabismus is warranted in the first instance. Children with neurological impairment have a higher incidence of strabismus and poorer surgical outcomes [24], which may be due to variability in strabismic angle and decreased fusional capacity [25]. However, they can benefit functionally and cosmetically from surgical correction. Under-correction of esotropia is recommended as it has a tendency to overcorrect later due to hypertonicity of horizontal extraocular muscles where the medial rectus is stronger than the lateral rectus muscle. On surgical weakening of the medial rectus muscle, hypertonicity of lateral rectus causes a consecutive exotropia [25]. Brodsky, *et al*. [24] recommend standard surgical correction for small exodeviations, but it may be progressively decreased for larger exodeviations when there is co-existing neurological impairment [25].

In ROP-treated eyes, around 20% develop amblyopia secondary to anisometropia and/or strabismus (***Web Table* III**). In our study, 20% eyes were amblyopic. Treatment comprises correction of the refractive-error, followed later by occlusion therapy or penalization of the better seeing.

Anterior Segment- associated Morbidity

Glaucoma and cataract are the major morbidities of the anterior segment in eyes with resolved ROP.

Glaucoma: Approximately 2% of ROP-treated eyes develop glaucoma by the age of 6 years [26]. There are several mechanisms, including secondary to laser-treatment which is more likely in preterm eyes with ROP on account of the anterior segment changes described above. Acute glaucoma can occur as early as two weeks after laser treatment, and is characterised by a hazy cornea due to raised intraocular pressure and shallow anterior chamber. The differential diagnosis is anterior segment ischemia in which the intraocular pressure is low. Laser-treatment can cause glaucoma as a result of inflammation, or acute angle closure glaucoma secondary to choroidal congestion and anterior displacement of the iris lens diaphragm [27].

Other mechanisms which can lead to glaucoma include neovascularization of the angle and iris in an untreated eye with advanced ROP, which may be another advantage of anti-VEGF preparations [16]. One must bear in mind that pupil dilation for retinal examination could result in acute angle-closure glaucoma in ROP patients, which can be avoided by prophylactic iridectomy in predisposed eyes [28]. Open angle glaucoma can also occur following vitrectomy for ROP, reported in 14.5% of cases [29].

Glaucoma is treated medically or surgically by surgical peripheral iridectomy, trabeculectomy or glaucoma implant surgery. Although rare, glaucoma can lead to the loss of what little remaining vision a child may have, rendering them totally blind.

Cataract: In the ETROP trial, 1.9% of eyes developed cataract by six months of age [30]. In ROP treated eyes, localized cataract can occur due to inadvertent injury with laser application [27]. The lens, which is relatively large in the small preterm eye, can also be damaged during intravitreal anti-VEGF injections, and can occur after vireo-retinal surgery for Stage 4 or 5 ROP. Cataract can also follow severe anterior segment ischemia, a rare entity that has been reported following intense laser-treatment of APROP [31].

Visually-significant cataracts can be a late manifestation of ROP in early adult life, as reported by Kaiser, *et al*. [32], where the mean age of individuals undergoing cataract surgery was 40.3 years. Unfortunately, cataract surgery in ROP eyes is complicated by retinal detachment in almost a quarter of cases, being far higher than in the general population. Individuals with cataract, who were previously treated for ROP, need careful and detailed pre-operative assessment, including ultrasound B scan, with detailed examination of the retina as soon as possible after cataract surgery to detect retinal breaks, peripheral scarring or macular dragging. Patients who were highly myopic are at even greater risk, but all should be counselled about the early symptoms of retinal detachment, and to have regular retinal examination.

Posterior Segment-related Morbidity

Structural changes in the retina of eyes with regressed ROP can cause unfavorable visual outcomes if the macula and posterior pole are involved. Between 4.6% and 33% of treated eyes develop macular dragging with or without retinal folds, due to peripheral retinal scarring and traction (***Web Table* III**).

Innocuous changes include vascular tortuosity (58%), narrowing of retinal vessels (53%), temporal crescent (7%), and optic disc drag in 19% of eyes. Changes in the retinal periphery include vitreous membranes (65%) and peripheral tractional retinal detachment (16%) (***Web Table* III**). In our study, posterior segment pathology was noted in 17 eyes (14.1% of ROP-treated eyes) with retinal, disc and macular pathologies occurring with equal frequency (***Web Table* III**).

Retinopathy of prematurity is, therefore, a condition

which can affect individuals until late in life, and life-long follow-up is required. For those with visual impairment use of low vision aid and visual rehabilitation should be done.

Other Visual Functions

Individuals treated for ROP have been reported to have reduced peripheral visual fields [33-36], which is less after laser-treatment than cryotherapy, which is more destructive. However, the degree of loss (average of 15 degrees) is not likely to be clinically significant. Contrast sensitivity was found to be reduced in prematurely-born children, with or without ROP or neurological deficit, in comparison to term infants and was found to be most reduced in cryo- treated eyes [35]. Children in the CRYO-ROP study were much more likely to have defects in color vision than the general population, reflecting changes at the macula [36].

SUMMARY

Although acute ROP is a condition which occurs very early in the life of preterm infants, it can have complications and implications which last a life-time. There is preliminary evidence that anti-VEGF agents may ameliorate some of the complications of laser treatment, particularly for the severest forms of ROP where extensive laser treatment is required.

The structural and functional outcomes in ROP-treated eyes include preventable conditions such as amblyopia, and treatable conditions such as refractive errors, strabismus, and retinal detachment. Children who are visually impaired can benefit from low vision services, and those who are blind can be offered rehabilitation. Many children born preterm, particularly those with birthweights less than 1000g, also have central nervous system abnormalities such as cerebral palsy, periventricular leukomalacia etc, which compound their disability.

Although most of the data on short and longer term outcomes of ROP come from high income settings where infants followed up were more preterm than in India, our study, although not large, confirms similar findings among ROP-treated children.

Infants treated for ROP as well as those who develop ROP not requiring treatment require follow-up to detect and manage complications, but there are no agreed recommendations on the timing [20]. The author recommends that the first examination by an ophthalmologist experienced in child-eye care be as early as 6 months after the ROP has regressed, to detect and treat refractive errors, strabismus and amblyopia. Infants who developed ROP that did not require treatment can be followed up later, and the age of 2.5 years has been recommended [20]. Infants who are visually impaired from retinal sequelae and/or neurological deficits should start vision stimulation and rehabilitation early, to try to reduce the developmental delay associated with severe visual loss of early onset. As the child reaches school-age, frequent change in spectacles, replacement of broken glasses and amblyopia therapy all need to be emphasized not only to parents but also to medical care providers. Lastly, particularly in a country like India where ROP is an emerging problem, awareness amongst ophthalmologists, physicians, pediatricians, teachers and therapists is mandatory to reduce the burden of blindness due to ROP and its sequelae.

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WEB TABLE I FUNCTIONAL AND STRUCTURAL OUTCOMES IN CLINICAL TRIALS OF RETINOPATHY OF PREMATURITY

	CRYO-ROP trial[38,39,40]	*ET-ROP trial*[14,21,41,42]	*BEAT-ROP*[16]
Gestatcorialage/Birthweight	<1251g	<1251g	≤30 weeks or ≤1500g
Follow up period	3.5 years for refractive errors[39]; 10 years for visual impairment[38]	4-6 years;[41]; 6 years[14]	2.5 years
Response rate	72.8% favourable retinal outcome in treated eyes[38]	74.9% in Type 1 ROP eyes (152/203 eyes)[42]	109/150 (73%)
Unfavourable Visual	Outcomes (VA< 6/60) 44.4% in treated *vs*. 62.1% in untreated eyes[38]	Type 1 ROP - 25.1% in treated *vs* 32.8% untreated eyes (P< 0.001)	
		Type 2 ROP - 23.6% in treated *vs* 19.4% in untreated eyes (P=0.18)[42]	No data - too young
Myopia	Mod ≤2D to <6D Treated 20.5% Untreated 15.5% High ≤6D Treated 37.7% Untreated 27.2%39 Lower BW and increasing severity of ROP were strong predictors of myopia and high myopia[40]	All treated eyes: Any myopia Type 1 - 67.8% and Type 2 - 75%; High myopia (>-5D): Type 1 - 37.2% and Type 2: 45% at 6 years of age[14]	Spherical equivalent (not retreated eyes) Laser: -7.34D (±7.44D) IVB : -1.36D (±3.34D)All zone 1 treated eyes: very high myopia ?8D: Laser 51.8% IVB 3.4%
Astigmatism	No data (There was a tendency for a greater proportion of treated eyes rather than of control eyes to have astigmatic errors of 1 D or more[38]	All treated eyes Any 42-52% High (>5D)18- 23% at 4-6 years[41].	No data
Amblyopia	No data	16.6% in treated *vs.* 19.6% in untreated eyes with bilateral symmetric disease[42]	No data
Unfavourable Retinal outcomes	27.2% in treated *vs* 47.9% in untreated eyes[38]	8.9% for early-treated eyes *vs* 15.2% for conventionally managed eyes for all high risk prethreshold. (p<0.001).[42]	No data
Strabismus	no data	42.2% at 6 years of age [21]	No data

GA = gestational age; BW = birth weight.

WEB TABLE II SEQUELA OF RESOLVED ROP IN TREATED AND UNTREATED EYES: VISUAL IMPAIRMENT AND REFRACTIVE ERRORS

Investigator/ year, No., (Mean follow up, y)	*Birthweight and gestational age (mean, range)*	*Visually impaired (VI) (%)*	*Myopia/ mean sph eqv (%)*	*Astigmatism (%), mean sph eqv, type (%)*	*Anisometropia (%)*
Shah, 2016[43] India 25 cases (6.91)	BW: 1509.6 (85-2080g GA: 32 (28-35) wks	8%	4.16% / -5.1D	89.6%, (-2.08), WTR: 83.7%	46.5% (27.9%>1D, 18.6% >2)
Hellegren KM, *et al* 2016[9] Sweden 434 cases (6.6)	BW: 348-1190g GA: 22-26 wks	2.1%: blind; 4.8%:VI	Refractive error: 29.7% Myopia>3D:4.1% Hyperopia >3D: 17.1%	>2D: 6.5%	>2D: 9.3%
Yang, 2013 and Yang, 2013[10,18] Taiwan, China 24 cases (9.2±0.5)	BW: 1256±315g GA: 28.80±2.35 wks	Mean VA:6/10; no visual impairment	93% / -4.49D >-6D myopia: 28.3%	98% >1D 80% >3D 50% WTR 98%	No data
Al-Otaibi, 2012[44] Saudi Arabia 57 cases (5.2 ± 2.5)	BW: 896.9 ±331.5 (400-1800)g GA: 26.5±3.1 (21-41) wks	30%	64% Mean: -6.69D; 28.9% had myopia > -6D	Not reported	Not reported
Yang, 2010[23] Taiwan, China 30 cases (7)	BW: 1213±302g GA: 28.7±2.6 wks	6.9%.1 eye (1.79%) with: unfavourable structural outcome	77% / 3.8D >6D myopia: 16.7%	>3D: 35%, Mean: -3.0 ± 1.6D	46.70%
Dhawan, 2008[45] India 93 cases (Median: 2)	BW: 1,137 (500-1800)g GA: 29.24 (28-34) wks	Not reported	80.30%	Not reported	12.90%
McLoone, 2008[46] Ireland 25 cases (11)	Mean values not quoted. All had BW <1500g & GA <31 wks	13.5% (7% unfavourable structural outcome)	50% overall. Treated: 35% >-4D. ROP resolved , no treatment: 21%, all <-1D	Not reported	Not reported
Ospina, 2005[47] Canada 21 cases (5 or more)	BW: 828 (530-1335)g GA: 25.7(23-35) wks	9.5% (3- CP, 1- RD)	62% / -4.9D >-4D in 47.6%	64.4% / -2D, WTR:96.3%	9.52% (diff of 1D)
Vijayalakshmi (unpublished data) 2015, India 66 cases (Median age : 3.5)	BW 1359.2 ±457.8 (545 -2700)g GA: 30.7±3.0 (25-40) wks	31.7%	Refractive errors in 67.2% of eyes. Simple myopia in 5%, hypermetropia in 3.4%	Myopic astigmatism - 65%, including high myopia 21.2%, hypermetropic astigmatism, 1.2%	7.6%

BW = birth weight; GA = Gestational age; wks = week; D = dioptre; CP = cerebral palsy; RD = retinal detachment; sph eqv =

WEB TABLE III SEQUELAE OF RESOLVED ROP IN LASER-TREATED AND UNTREATED EYES: OTHER CONDITIONS

Investigator/ year	*Amblyopia (%)*	*Strabismus (%)*	*Posterior segment findings*	*Authors comments (type of ROP)*
Shah, 2016[43]	No data	No data	Disc dragging 2.1%	Most treated eyes had favourable anatomical and visual outcomes. Anisometropia and high refractive error are common causes of visual impairment. Long-term follow-up is mandatory (Zone 1 AP-ROP)
Hellegren, 2016[9]	No data	17.4% (n:68): Strabismus 79.4% (n:54): Esotropia 20.6% (n:14): Exotropia	No data	EPT children at 6.5 years of age, major eye and visual problems were frequently found. Treatment-requiring ROP was a stronger impact factor than GA on visual impairment and strabismus, but not on refractive errors, as a whole. In modern neonatal intensive care settings, ophthalmologic problems continue to account for a high proportion of long-term sequelae of prematurity.
Yang, 2013[10]and[18]	Total 5 (20.8%) 3 anisometric 1 strabismic 1 high myopia	25% (3/6 Esotropia)	Macular dragging 2% (1 eye)	Higher rate and severity of astigmatism and myopia in laser-treated eyes with threshold ROP than term controls. Refractive status reflects altered anterior segment.
Al-Otaibi, 2012[44]	Not reported	54.4% of which 43.9% had esotropia	Macular dragging or retinal detachment 33%	Most diode laser-treated eyes had favourable visual and structural outcomes. Strabismus and high refractive errors are important causes of visual impairment.
Yang, 2010[23]	53.3% (16 children)	30% - a/w PVL 5 esotropia, 4 exotropia.	Macular dragging 1.7% (1 eye)	Strabismus significantly associated with PVL (p=0.002)
Dhawan,2008[45]	No data	16.13% 8 esotropia 7 exotropia	Tortuous vessels: 58.2%, Narrow vessels: 53.3%, Temporal crescent: 7.1%, Disc drag: 18.5%, Macular heterotopia: 14%, Vitreous membranes: 65%, Peripheral RD:16.3%	Eyes treated with laser for threshold ROP develop retinal residua, refractive errors, and ocular motility disorders. Frequent and long-term follow-up required.
McLoone, 2008[46]	20% 4 strabismic, 1 aniso-metropic	32% strabismus, 4 esotropia, 4 exotropia	2 total RD, 1 macular fold	Good long term visual outcome in laser treated eyes with favourable structural outcomes (Threshold ROP).
Ospina, 2005[47]	19% 4 mixed, 1 strabismic	28.50%	Straight vessels: 21.4%; Macular distortion: 7.1% Diisc hooding : 4.7%	Retinal scarring and RD relatively rare causes of visual morbidity ?5 years after laser. Neurological sequelae of extreme prematurity and amblyopia important causes (Threshold ROP)
Vijayalakshmi (unpublished data) 2015	20%	25% (n:30) strabismus 14 Esotropia 16 Exotropia	Structural pathology in 17 eyes (14.1%); RD (5), macular drag and degeneration (3), disc pathology (5) choroidal scarring (2) peripheral glial tissue (1), ERM (1)	ROP affected more mature children with late presentation (>stage 4, 8.3%). 24/66 children had vision impairment, 20 of whom had developmental delay. National coordination is needed for early detection, management and long term follow up of all premature infants discharged from NICU.

RD = retinal detachment; a/w = associated with; PVL = periventricular leucomalacia; CP= cerebral palsy; IVH= intraventricular haemorrhage; ERM = extra retinal membrane