Original Article

Refractive, sensory, and biometric outcome among retinopathy of prematurity children with a history of laser therapy: A retrospective review from a tertiary care center in South India

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Purpose: Ocular morbidities like high refractive error, strabismus, and amblyopia are common among laser-treated retinopathy of prematurity children (ROP). Long-term optical status and refractive outcomes including the sensory outcomes were less investigated in these children from this region. The purpose of our study is to evaluate the long-term outcome (refractive, biometric profile, sensory) of treatment for ROP using laser. **Methods:** This study is a retrospective, cross-sectional, observational, and intervention research among 6–15-year-old children who underwent laser for ROP with a minimum of 6-year follow-up. **Results:** Eighty lasered eyes of 41 children were assessed. Mean age was 9.71 years (±3.39). Seventy-three eyes (91.2%) achieved visual acuity better than 20/40. The mean visual acuity in LogMAR was 0.18 (20/30). The mean spherical equivalence was −5.29 D ± 4.9. Mean astigmatism measured was −1.53 DC (range: +0.50 DC to −4.5DC). Fifty-three eyes (66.25%) had significant astigmatism. The mean axial length was 23.5 ± 1.35 (21–26) mm. Mean lens thickness was 3.76 ± 0.30 (3.03–4.34) mm. Correlation analysis among the low and high spherical equivalent group signified that axial length (*P* value = 0.001), visual acuity (*P* value = 0.0002), and myopic shift (*P* value = 0.0006) were found to be statistically significant. Stereopsis better than 480 s of arc for near was observed in 41% children. Structural posterior pole sequelae developed in 3 eyes (3.75%). **Conclusion:** A significant number of children with high myopia, astigmatism, and strabismus had satisfactory visual outcome observed at long-term follow-up after treatment for ROP using laser. Our study revealed that myopia was influenced by an increase in axial length than the lens thickness.

Key words: Myopia, ocular biometry, refractive outcome, retinopathy of prematurity, sensory outcome

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Retinopathy of prematurity (ROP) is a widely recognized cause of visual impairment in premature infants that occurs due to abnormal retinal vasculature at the boundary of vascularized and avascular peripheral retina.[1] In 2005, Gilbert *et al*. reported the prevalence of ROP-related blindness in India to be approximately 0.2% of the worldwide burden.[2] Advancements in infant healthcare has led to an increased survival of prematurely born infants in the middle-income countries. Severe ROP is often encountered in babies weighing greater than 1250 g at birth in developing countries.[3] In 2010, Blencowe *et al*. estimated about 20,000 premature survivors with severe visual impairment and blindness worldwide.[4] It is well established that prematurity, low birth weight, and ROP increases the risk for myopia. Laser photocoagulation reduces the morbidity arising from ROP and results in successful anatomical outcome. It acts by ablating abnormal retinal tissue and stops release of angiogenic factor.[5] Ophthalmic morbidities such as refractive error, strabismus, and amblyopia are common among this subset of children.[6-8]

Long-term optical status and refractive outcomes in children with ROP who underwent laser treatment were investigated in the past; however, a comprehensive way of analyses with the addition of sensory outcomes have been less investigated and reported from this region. Therefore, this study aimed at analyzing the refractive, ocular biometric profile and sensory outcome among children who had a minimum of 6 years of post-laser follow-up.

Methods

This study was a retrospective, cross-sectional, follow-up study of intervention in children aged 6–15 years who underwent laser treatment for ROP. The study was approved by the institutional ethics committee and adhered to the provisions of the declaration of Helsinki. We reviewed the case records of all children who visited our paediatric ophthalmology clinic between December 2017 and May 2018 with a prior history of laser treatment for ROP with a minimum of 6 years post-laser

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follow-up. We excluded patients who either spontaneously regressed and those who underwent surgery (vitrectomy). Data collected included sex, gestational age at birth (GA), birth weight, oxygen exposure, stage and zone of ROP involvement, the presence of aggressive posterior ROP (APROP), plus disease post conception age at laser treatment, unilateral or bilateral treatment, type of treatment received, age at regression of disease, and the spherical equivalence at 1 year of age. None of the patients in the study group received anti-VEGF along with laser therapy.

At presentation, all patients aged 6 years and above underwent a complete ophthalmological evaluation including best-corrected uniocular Snellen's visual acuity and dynamic refraction. Sensory evaluation included binocular single vision and stereopsis. Measurement of ocular deviation was done using prism bar cover test. Color vision using Ishihara chart and contrast sensitivity (CS) using The Mars Letter Contrast Sensitivity Test were assessed. Refractive error was checked after dilatation with 1% cyclopentolate. Refractive error was converted to spherical equivalent (SE) and defined as spherical error + half cylindrical error. Negligible refractive error was SE of ± 0.5D. Myopic shift was calculated using the difference between the spherical equivalence at present evaluation and spherical equivalence at 1 year of age; this divided by age gives myopic shift/year. Anisometropia was defined as the difference of SE between the eyes of ≥1.5 D. Following cycloplegia, ocular biometry was done using IOL master (Carl Zeiss Germany), in which the horizontal white to white corneal diameter, corneal power (average of the K1 and K2 reading), anterior chamber depth, axial length, and lens thickness were measured. The anterior and posterior segment were examined for structural sequelae. The stage and severity of ROP were classified according to the International Classification of ROP.[9] The indication for laser treatment was as per the Early Treatment for Retinopathy of Prematurity Cooperative Group (ET-ROP).[10]

Statistical analysis

Data from each eye were taken as an independent variable. Mean, median, range, and standard deviations were calculated for the demographic, refractive, biometric, and sensory outcome data. To investigate the linear relationship between each refractive component to gestational age and birth weight to determine the strength of association between the two sets of numerical scores Spearman correlation test was used. *P* value less than 0.05 considered statistically significant.

Student's *t*-test/Mann–Whitney U-test was used to determine the significant difference between two quantitative variables.

Results

Demographic characteristics

Eighty lasered eyes of 41 children met the inclusion criteria. They presented at a mean age 9.71 (±3.39) years (range, 6–15 years). There was no significant sex difference among the study groups (M:F, 51.2%:48.8%). Most children (39/41) underwent laser photocoagulation for ROP on both eyes (95.1%), whereas the remaining 2/41 underwent uniocular (4.9%). Their mean gestational age was 30.51 weeks ± 2.01 (26–35) weeks, and the mean birth weight was 1430.37 ± 318.11 (800–2250) g. Our study group comprised 48.7% babies with gestational age of ≤30 weeks, whereas 51.3% were >30 weeks of gestation. 61.3% had a birth weight ≤1500 g and 38.7% had a birth weight >1500 g. Among the study group, 78% of the infants were exposed to oxygen therapy while 22% did not. Duration and concentration of the therapy were not documented in patient's records; therefore, this factor was omitted from data analysis.

Of the 80 eyes evaluated, Zone I involvement was present in 28 (35%) and Zone II in 52 (65%). APROP was present in 26 (32.5%) and plus disease in all patients. Their mean post conception age at which laser photocoagulation was performed was 35.39 (range, 30–42) weeks. The mean number of laser spots applied was 2262 (range, 743–5623) spots. The mean time for regression of ROP following treatment was 28.60 (range: 7–112) days.

Refractive outcome

Refractive outcomes are depicted in Table 1 under mean or median column. The mean visual acuity in LogMAR was 0.18 (20/30) (range: 20/125–20/20). Seventy-three eyes (91.2%) had visual acuity better than or equal to 20/40 and 25 eyes (31.25%) had visual acuity of 20/20. Seven eyes (8.8%) had satisfactory visual acuity between 20/40 and 20/200. None of the patients had unsatisfactory visual acuity worse than 20/200. Seventy-three eyes (91.25%) had refractive error. The mean spherical equivalence was −5.29 D ± 4.9 (range, +0.75 to −18.5 D). Seventy-one eyes (88.75%) had a myopic refraction. Forty eyes (50%) had low myopia (≤6 D) while high myopia (>6.0 D) was seen in 31 eyes (38.75%). Two (2.5%) eyes had hyperopia. Mean astigmatism measured was –1.53 DC (range: +0.50 DC to −4.5DC). Fifty-three eyes (66.25%) had significant astigmatism. With the rule astigmatism, against the rule astigmatism, and oblique astigmatism were present in 62.5%, 8.75%, and 16.25% eyes, respectively. Fifteen eyes (36.58%) had an anisometropia (range: 1.5–7.5 D). Seven (8.8%) eyes had emmetropia. The mean CS was 1.64 log CS units. Color vision

Table 1: Comparison of gestational age, birth weight, zones involved and presence of APROP with refractive and biometric outcomes

Outcomes	Mean or median	Gestational age (*P*)	Birth weight (*P*)	Zone (*P*)	APROP (*P*)
Visual acuity in (Median logMAR)	0.18 (6/9)	0.099[b]	0.012[b,#]	0.149[b]	0.086[b]
Spherical equivalent Mean (SD)	−5.28DS (4.72)	0.038[b,#]	0.035[b,#]	0.224[b]	0.488[b]
Astigmatism Mean (range)	−1.53DC (0.5-−4.5DC)	0.457[c]	0.261[c]	0.423[c]	0.331[c]
Myopic shift (Median)	0.29	0.016[b,#]	0.325[a]	0.250[b]	0.655[b]
Axial length Mean (SD)	23.50 (1.40)	0.127[a]	0.710[a]	0.445[a]	0.948[a]
Lens thickness Mean (SD)	3.81 (0.31)	0.322[a]	0.964[a]	0.252[a]	0.050[a]

[a]Independent *t*-test; [b]Mann-Whitney U-test, [c]Fisher's exact test, [#]Statistically significant; *P*<0.05. SD: Standard deviation; DS: Dioptre sphere; DC: Dioptre cylinder; APROP: Aggressive posterior retinopathy of prematurity

was normal in 77 (96.25%) children. The mean SE at 1 year of age was −2.28 (range, +4 to −12.5), the mean myopic shift was –2.99 D (range, +0.25 to −17.50 D) in the study group. Mean myopic shift per year −0.29 D/year (IQR: 0.17–0.53 D).

Ocular biometric profile

Table 1 also depicts the mean axial length 23.5 mm ± 1.35 (range, 21–26) and mean lens thickness 3.76 mm ± 0.30 (range, 3.03–4.34). The mean corneal refractive power was 46.3 D and the mean horizontal white to white corneal diameter was 11.8 mm. The mean anterior chamber depth was 3.1 mm.

Of the two patients who received unilateral laser treatment, in one child, the nonlaser treated eye was less myopic (difference of SE 2.5 D), similar visual acuity, 0.5 mm lesser axial length, and 0.20 mm lesser lens thickness in comparison to the laser treated eye. In the other patient, the nonlaser treated eye was more myopic (difference of SE, 1 D), 1.15 mm more axial length and 0.25 mm lesser lens thickness in comparison to the laser treated eye.

Mann–Whitney U-test results are depicted in Table 1. It showed a correlation between gestational age (≤30 weeks and >30 weeks) with SE (*P* value = 0.038) and myopic shift per year (*P* value = 0.016) denoting that there is a significant difference between the gestational age groups. This indicated that high myopia refraction is seen among children with low gestational age and they had a higher myopic shift. Similar analysis results depicted in Table 1 between birth weight (≤1500 g and >1500 g) showed that the *P* value had significant difference in SE (*P* value = 0.035) and logMAR visual acuity (*P* value = 0.012), denoting lower birth weight group had higher SE and higher logMAR. Student's *t*-test when performed between eyes with APROP and without APROP showed the lens thickness with a *P* value of 0.050 [Table 1].

Table 2 depicts the correlation of gestational age and birth weight with refractive components analyzed using spearman rank order correlation. There was a correlation between gestational age and spherical equivalent (rho = 0.22, *P* value = 0.045) suggesting that lower gestational age children had higher SE. Also, there was correlation between gestational age and axial length (rho = −0.22, *P* value = 0.048) indicating that lower gestational age children developed longer eyes. While correlating between birth weight and visual acuity (rho = −0.23, *P* value = 0.040) suggests that higher the birth weight, better the visual acuity.

Mean axial length among the low (≤6 D) and high (>6 D) SE group are 22.73 mm and 24.79 mm, respectively, as shown in Table 3. Moreover, Student's *t*-test and Mann–Whitney U-test when performed between low SE groups and high SE groups signified that axial length (*P* value <0.001), visual acuity (*P* value = 0.0002), and myopic shift (*P* value = 0.0006) were found to be statistically significant [Table 3].

Table 2: Correlation analysis of gestational age and birth weight with refractive components

Refractive components	Gestational age		Birth weight	
	Correlation	*P*	Correlation	*P*
Visual acuity	−0.19	0.088	−0.23	0.040#
Spherical equivalent	0.22	0.045#	0.21	0.057
Lens thickness	−0.09	0.425	−0.11	0.319
Axial length	−0.22	0.048#	−0.06	0.628
Myopic shift	−0.19	0.096	−0.18	0.108
Astigmatism	−0.01	0.914	0.03	0.779

Spearman rank order correlation; #Statistically significant; $P<0.05$

Sensory outcome

Fifteen children (36.5%) had strabismus [1 (2.4%) esotropia, 13 (31.7%) exotropia, and 1 (2.4%) hypertropia]. Among the children with exotropia, the mean deviation for distance and near were 25 prism D and 18 prism D, respectively; mean age at which exotropia was detected was 41.6 months (range, 20–84 months). Of them, five children required to do occlusion therapy (two strabismic amblyopia and three anisometropic amblyopia). Five children had intermittent exotropia and were advised orthoptic exercise. One child underwent surgical squint correction (unilateral recession/resection procedure) at 6 years of age and two other children with alternate exotropia were advised surgical squint correction. Of the 41 children, 9 (10.6%) had amblyopia. Six had anisometropia associated with amblyopia, two with strabismic amblyopia, and one had isometropic amblyopia. In the study group, 34 children (82.9%) and 28 children (68%) had binocular single vision for near and distance, respectively. Seventeen children (41%) had stereopsis better than 480 s of arc for near. Six (14.6%) had a best stereopsis of 60 s of arc.

Structural outcome

Structural sequelae developed in 3 eyes (3.75%). Among them one had peripheral traction membrane and developed very high myopia and strabismus with satisfactory visual acuity of 20/63. One child (both eyes) had visually insignificant cataract with high myopia and isometropic amblyopia with a visual acuity of 20/80. This patient was kept on observation as the density of cataract was not contributing to vision loss. None of the children had glaucoma.

Discussion

The study depicted the long-term outcome in children treated for ROP with laser therapy. Comparison among the studies[11-17] about the patient characteristics are tabulated in Table 4. All the studies including the present study had much higher mean birth weight and mean gestational age compared to ETROP cohort [(703 g) and (25 weeks)].[10] Yang *et al*. reported mean LogMAR visual acuity of 0.20 (20/32) similar to our results.[16] In a study done by Shah *et al*. on Zone 1, APROP reported 10.41% with 20/20.[14] The reasons for our good visual outcome could have been due to early referral, timely management, and faster regression of disease (mean regression of disease being 28 days), which in turn also resulted in good structural outcome. Katoch *et al*. in their study concluded that the risk factors for myopia were due to greater number of clock hours of ROP, greater number of laser spots, and a longer time to regression of ROP.[18] In prematurely born infants, gestational age and birth weight cannot be controlled. Only strict neonatal care, early treatment for ROP, and timely referral can control the severity of disease, reduce myopia, and provide good visual outcome.

Like other studies[11,13,14,17] ours also showed a significant number of eyes with predominantly high myopic SE and astigmatism [Table 4]. Many authors have concluded myopia

Table 3: Comparison between low and high SE group with refractive and biometric outcomes

Refraction and Biometric outcomes	Spherical equivalent		*P*
	Low SE (*n*, %=50, 62.5%)	High SE (*n*, %=30, 37.5%)	
Visual acuity			
Median logMAR (Snellen's equivalent)	0.18 (6/9)	0.18 (6/9)	0.0002#
Myopic shift			
Median DS	0.22	0.44	0.0006#
Axial length			
Mean (SD) mm	22.73 (1.10)	24.79 (0.74)	<0.001#
Lens thickness			
Mean (SD) mm	3.83 (0.30)	3.77 (0.33)	0.456

SD: Standard deviation; SE: Spherical equivalence; DS: Dioptre sphere; mm: millimetre; #Statistically significant; $P<0.05$

Table 4: Comparison between studies: Patient demography, refractive, and biometric outcomes

Studies in comparison / Parameters	Connolley *et al.*[11] (2002)	McLoone *et al.*[12] (2006)	Yang *et al.*[13] (2012)	Shah *et al.*[14] (2012)	Nguyen *et al.*[15] (2015)	Stoica *et al.*[16] (2016)	Kaur *et al.*[17] (2017)	Present study (2018)
No. of eyes	20	16	46	48	100	96	72	80
Mean age at study (years)	10	11.1	9.2	6.9	5	-	7.37	9.71
Mean gestational age (weeks)	-	26.6	28.8	31.7	29.88	29.37	29.01	30.51
Mean birth weight (g)	-	890	1256	1572	1426	1348	1262	1430
Mean BCVA (logMAR)	-	0.17	0.20	-	-	0.15	0.29	0.18
Mean SE (D)	−4.48	−2.33	−4.49	−5.62	−2.87	−4.12	−4.50	−5.29
Occurrence of myopia (%)	-	50	93	93.75	59	70.83	75	88.75
Mean astigmatism (D)	1.32	1.38	3.47	−2.08	+1.63	-	−1.2	−1.53
Occurrence of astigmatism (%)	-	50	97.7	48.8	49	76	30.5	66.25
Mean axial length (mm)	22.89	22.81	23.32	-	-	-	20.35	23.50
Mean AC depth (mm)	3.44	3.38	2.91	-	-	-	2.95	3.10
Mean corneal power (D)	46.68	45.24	-	-	-	-	45.8	46.30
Mean lens thickness (mm)	3.95	-	3.94	-	-	-	4.33	3.76

to be associated with ROP laser treated than non-ROP infants and spontaneously regressed ROP cohort.[15,17,19] Choi *et al*. concluded that myopia begins to appear at 6 months of age and its severity increases between the ages of 6 months and 3 years, and eyes with cicatricial retinopathy tended toward myopia.[20] ETROP findings suggested that increased myopia in fact is due to more severe ROP rather than any direct effect of the laser treatment.[21] The reason for developing myopia in laser treated eyes seems to be controversial. It is proposed that high myopia is due to steep keratometry, greater lens thickness, forward position of the lens center, and shallower anterior chamber.[12,13,17,20] Fielder *et al*. had suggested that the ROP insult retards that part of the globe which is undergoing maximal growth, and this effect will in turn mechanically inhibit anterior segment development.[22] It was also argued that the ablated retina following laser therapy hampers ocular growth in the posterior segment. This could trigger overcompensation of the anterior chamber. Yang *et al*. hypothesized that there is incomplete postnatal development of the cornea, anterior sclera, and anterior segment in the premature infants.[13]

Biometric outcomes when compared with other studies[11-13,17] showed increased axial length, shallow anterior chamber depth, and increased lens thickness [Table 4]. Laws *et al*. indicated a negative correlation between the severity of ROP and axial length, suggesting that changes in axial length were not caused by ROP but by prematurity.[23] Choi *et al*. found an average axial length in emmetrope, low myopia, and high myopia as 21.96 mm, 22.74 mm, and 24.77 mm,[20] which were similar to our study findings. Lee *et al*. reported that the average axial length in emmetropia of 6 year olds to be 22.18 mm.[24] It is not possible to directly correlate statistically with the results of Lee *et al*.; however, the present study showed that there is an increased axial length among the premature laser treated infants and it was statistically significant (P = 0.001) with a significant myopic shift (P = 0.0006), as depicted in Table 3. Most studies reported the increased lens thickness to be a contributory factor for myopia in laser-treated ROP eyes.[17,25] Our study revealed that myopia was influenced by an increase in axial length than the lens thickness. Connolly *et al*. found that laser-treated eyes were significantly less myopic than cyrotherapy-treated eyes and that the lens power seemed to be the predominant factor contributing to the excess myopia.[11]

Subtle color vision and contrast sensitivity deficits were found among preterm and severe ROP babies.[26] Mean contrast sensitivity was reported as 1.28 log CS units according to Kaur *et al*.[17] In a study by Bonotto *et al*. on preschool laser-treated ROP children, normal CS and color vision was reported among 66.67% and 100%, respectively.[27] Majority of our children had best CS and color vision. There is a paucity of studies about the sensory outcome in children laser treated for ROP.[15,17]

Lower stereoscopic resolution and binocularity was observed among premature infants after ROP treatment which varied with ROP severity. Bonotto *et al*. reported that none had good stereopsis.[27] Present study also reported excellent sensory outcome. Other studies reported the percentage of strabismus among laser-treated ROP eyes ranged between 10% and 30.5%.[13,15,17] The current study showed exotropia in a majority of the children.

The first limitation of this study was its retrospective nature that induces inherent sampling and observational bias. Second, it lacked a control group. It would have been more informative if it could have been compared with a similar cohort for eyes requiring no laser after prematurity. Randomized control trials would provide more light into the unknown aspects of why high myopia is common in these eyes.

Conclusion

Primarily, the study indicated a good refractive outcome in terms of best-corrected visual acuity, spherical equivalence, and satisfactory sensory outcome, indicating binocularity and effective treatment of amblyopia and a favorable structural outcome in ROP children treated with laser. Very few studies have focused on these parameters and provided a long-term outcome. Second, the present study corroborated its findings with other studies in showing high myopia, astigmatism, and strabismus in laser-treated eyes. Third, the study revealed that myopia was influenced by an increase in axial length than the lens thickness among patients

With the epidemic of premature survivals, the burden of ROP will be on a steady rise, and a lack of awareness about ROP among pediatricians is a real concern. The present study results are likely to increase the awareness about the long-term challenges regarding refractive error. A lower threshold for spectacle prescription for this category of children is also recommended. Timely and meticulous long-term follow-up is mandatory in these children.

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Conflicts of interest

There are no conflicts of interest.

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