

Outcome of Laser Photocoagulation for Retinopathy of Prematurity in a Tertiary Care Setting in Trivandrum, Kerala

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ABSTRACT

Introduction: Retinopathy of prematurity (ROP) is a disease affecting the retina of premature infants due to retinal neovascularization and the spectrum of outcome findings in ROP ranges from the most minimal sequelae without affecting vision in the mild cases to bilateral, irreversible and total blindness in more severe cases. This study aimed to evaluate the functional and structural outcome in preterm infants who received laser photocoagulation for retinopathy of prematurity.

Material and Methods: A hospital based descriptive study was conducted among 24 preterm infants with retinopathy of prematurity who received laser photocoagulation treatment after obtaining parental consent in the Retina clinic, Regional Institute of Ophthalmology, Trivandrum. Screening examination was done at 34 weeks or 4 weeks postnatal whichever was earlier. Those infants who were detected to have ROP and were given laser photocoagulation by the ophthalmologist were followed up till retina becomes stable / ROP regresses. Thereafter follow up examinations were performed at 3 months, 6 months and 10 months. Structural outcome was classified as favourable and unfavourable. Visual or functional outcome was assessed by noting the fixation pattern, ocular alignment for strabismus and by performing cycloplegic refraction (retinoscopy) to rule out refractive errors. Data was entered into excel sheet and statistical analysis was done using SPSS trial version.

Results: The study was conducted in 31 preterm infants with Retinopathy of Prematurity who underwent laser photocoagulation in Regional Institute of Ophthalmology Trivandrum. The structural and functional outcome was assessed at 3 months, 6 months and 10 months. Of the 62 eyes of 31 infants, stage 2 and 3 comprised 48.4% each. 3.2% of eyes had stage 1 disease affecting zone 1. None had stage 4 or 5. Of the 62 eyes, majority had zone 2 disease (83.9%). Only 10 eyes had zone 1 disease. Out of the 60 eyes, 54 eyes had a favourable structural outcome at 3 months.

Conclusion: The incidence of favorable structural outcome in our study was 90%. Low gestational age and low birth weights were associated with an unfavorable structural outcome. There is a high prevalence of refractive errors in our study group accounting for about 71.5% at 6 months.

Keywords: Retinopathy of Prematurity, Laser Photocoagulation, Retinal Neovascularization, Retrolental Fibroplasia, Oxygen Therapy

ischemia and subsequent development of neovascularization. The spectrum of outcome findings in ROP ranges from the most minimal sequel without affecting vision in the mild cases to bilateral, irreversible and total blindness in more severe cases. The retinopathy was first reported by Terry in 1942 and suggested that in this disorder, retrolental fibroplasia appeared to develop after birth since several babies who manifested the disease had normal examinations shortly after birth¹.

Retinopathy of prematurity (ROP) is a leading cause of blindness among children in areas of the world that provide neonatal intensive care services to premature newborns. Among the preventable causes of childhood blindness (57%), ROP figures very high². Furthermore, developing countries are witnessing an increase in retinopathy of prematurity (ROP); therefore, ROP has now become a leading cause of childhood blindness worldwide. Asians also have an increased risk of ROP. In India, the incidence of ROP is estimated to be about 24% and in children less than 1500g almost 38 percent have chance of developing any stage of ROP and 7 – 16 % chance of developing threshold ROP or blinding ROP.³

National Cooperative Study of Oxygen and ROP in the mid 1950s⁴ established the link between excessive Oxygen therapy and ROP which led to severe restriction of oxygen administration in premature babies which in turn resulted in increased mortality. This observation led to the more liberal use of oxygen and a resurgence of ROP known as the second epidemic.

No standard guidelines existed for the treatment of ROP before the multicenter trial Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP Study)⁵ which established that the treatment with cryotherapy for threshold ROP reduced the incidence of unfavourable outcome. Laser photocoagulation has replaced cryotherapy as the established

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INTRODUCTION

Retinopathy of prematurity is a disease affecting the retina of premature infants. Its key pathological change, retinal neovascularization appears to be associated with local

treatment for ROP in most centres. The guidelines for treatment changed after the early treatment of Retinopathy of Prematurity Study (ETROP Study) and the follow up reported a better structural outcome. Cryotherapy to the avascular anterior retina in ROP eyes with threshold disease has been demonstrated to reduce by approximately half the incidence of an unfavorable outcome such as macular dragging, retinal detachment, or retrolental cicatrix formation. The treatment of choice for ROP has long shifted from cryotherapy to peripheral diode laser photocoagulation soon after clinical studies showed that laser therapy is superior to cryotherapy. Laser photocoagulation is simpler to administer than cryotherapy in experienced hands and does not require conjunctival incision for posterior disease⁶⁻¹².

Most ophthalmologists prefer laser therapy to retinal cryoablation because of its superior clinical efficacy and cost effectivity.^{13,14} This study aimed to evaluate the functional and structural outcome in preterm infants who received laser photocoagulation for retinopathy of prematurity in RIO Trivandrum.

MATERIAL AND METHODS

The hospital based descriptive study was conducted in preterm infants who developed retinopathy of prematurity and were given laser photocoagulation treatment at Retina clinic, Regional Institute of Ophthalmology, Trivandrum for a period of two years (June 2014 to January 2016). All infants who underwent laser photocoagulation for ROP during the study period whose parents were willing to participate and come for follow up were included in the study. Minimum sample size was calculated as 24, calculated using the equation $4pq/d^2$ where $p=91$ (the percentage of favorable structural outcome¹⁵).

Screening examination was done at 34 weeks or 4 weeks postnatal whichever was earlier. Those infants who were detected to have ROP and were given laser photocoagulation by the ophthalmologist were followed up till retina becomes stable / ROP regresses. Thereafter follow up examinations were performed at 3 months, 6 months and 10 months.

Outcome measures:

Structural outcome was classified as favorable and unfavorable. Favorable outcome includes (1) completion of full retinal vascularization (2) progression of vascularization into zone 3 without previous zone 2 (3) PCA 45 weeks without developing at least type 2 ROP. Unfavorable outcome includes¹⁵ 1) posterior retinal fold involving macula 2) retinal detachment involving macula 3) fibrosing tissue obscuring view of posterior pole. Visual or functional outcome was assessed by noting the fixation pattern, ocular alignment for strabismus and by performing cycloplegic refraction (retinoscopy) to rule out refractive errors. Refractive outcome was assessed after cycloplegic retinoscopy. In our study refractive errors have been classified as follows (in terms of the spherical equivalent calculated from the retinoscopy):

Hypermetropia :> 4D (Diopters)¹⁶

Emmetropia: 0 to 4 D

Myopia has been further classified as¹⁷

- Low myopia: 0 to -3D
- Moderately myopia: -3 to -6D
- High myopia: > -6D

STATISTICAL ANALYSIS

Data was entered in to excel sheet and statistical analysis was done using SPSS software. Percentage and frequency of each outcome was calculated. The association of various factors with the outcome was considered significant if the p value is less than 0.05.

RESULTS

1. General Characteristics of ROP among Study Participants

The study was conducted in 31 preterm infants with Retinopathy of Prematurity who underwent laser photocoagulation for the same in Regional Institute of Ophthalmology (RIO). The structural and functional outcome was assessed at 3 months, 6 months and 10 months. The structural outcome was considered favorable if there is regression of ROP, vascularisation reaching up to periphery of retina. An unfavorable outcome was defined as (1) a posterior retinal fold involving the macula/macular drag (2) a retinal detachment involving the macula (3) retrolental tissue or "mass" obscuring the view of the posterior pole. Those requiring vitrectomy or scleral buckle were also considered as unfavourable outcome. Functional outcome was assessed by noticing visual behavior, refractive errors and sequel like strabismus or nystagmus. The findings of the study are presented below

A total of 31 infants (62 eyes) were enrolled into the study over a period of one year. Among these 31, one baby was not brought for follow up and was dropped from the study. Thus a total of 30 infants were studied and followed up for a period of 10 months. Among them 16 (51.6%) were male and 15 (48.4%) were females.

Of the 31 babies majority belonged to 28-30 weeks gestational age (38.7 %). The gestational age ranged from 26 weeks to 38 weeks. The mean gestational age was 30.2 weeks (SD 1.8 weeks). Among the babies majority was in <1.5kg category (80.6%). The birth weight ranged from a minimum of 850 gm to maximum of 1.88 kg. The mean birth weight was 1.24 kg (SD 0.26 kg) (Table-1).

Majority of infants were diagnosed to have ROP at a post conceptional age (PCA) of 32-34 weeks. Age of detection of ROP ranged from as early as 30 weeks to as late as 38 weeks (Table-1).

Most of the babies underwent laser photo coagulation after 34 weeks since most of the babies detected with ROP developed threshold disease after 34 weeks of post conceptional age. All the infants had history of respiratory distress at birth (RDS) and all of them had neonatal ICU admission. All babies were given supplemental oxygen. 3% of the infants had neurological disorder like seizure or intra cranial hemorrhage. 54.8% had neonatal sepsis.

Factors	Category	Frequency	Percentage (%)
Gestational Age of the study participants	< 28 weeks	2	6.5%
	28-30 weeks	12	38.7%
	30-32 weeks	9	29%
	32-34weeks	8	25.8%
Post conceptional age of diagnosis	30-32 weeks	1	3.2%
	32-34 weeks	13	41.9%
	34-36 weeks	8	25.8%
	36-38 weeks	9	29%
Post-conceptional age at which treatment started	30-32 weeks	1	3.2%
	32-34 weeks	9	29%
	34-36 weeks	8	25.8%
	36-38 weeks	13	41.9%
Total		31	100

Table-1: Profile of study participants based on Gestational age, post conceptional age at diagnosis and treatment (n-31)

Stages of ROP	Frequency	Percentage (%)
Stage 1	2	3.2%
Stage 2	30	48.4%
Stage 3	30	48.4%
Total	62	100%

Table-2: Distribution of Retinopathy of Prematurity stages among the study participants (n-62)

Structural Outcome	Frequency	Percentage (100%)
Favourable	54	90.0%
Unfavourable	6	10.0%
Total	60	100.0%

Table-3: Distribution of structural outcome of retina on study participants at 3 months (n-60)

Factors	Category	Favourable outcome		Unfavourable outcome		Total (%)	
		N	%	N	%	N	%
Gestational Age of the study participants	< 28 weeks	4	100	0	0	4	100
	28-30 weeks	18	81.8	4	18.2	22	100
	30-32 weeks	16	88.9	2	11	18	100
	32-34weeks	16	100	0	0	16	100
Birth weight	<1.5 kg	42	87.5	6	12.5	48	100
	>1.5 kg	12	100	0	0	12	
Involvement in clock hours	<6 hours	14	93.3	1	6.7	15	100
	>6 hours	40	88.8	5	11	45	
Stage of ROP	Stage 1 or 2	30	93.7	2	6.3	32	100
	Stage 3	24	85.7	4	14.3	58	

Table-4: Distribution of structural outcome of retina with gestational age, Birth weight and involvement in clock hours (n-60)

Visual behaviour	Frequency	Percentage
Favourable	58	96.7%
Unfavourable	2	3.3%
Total	60	100

Table-5: Distribution of functional outcome among the study participants (n-60)

Of the 62 eyes of 31 infants, stage 2 and 3 comprised 48.4% each.3.2% of eyes had stage1 disease affecting zone 1.None had stage 4 or 5 (Table-2). Of the 62 eyes; majority had zone 2 disease (83.9%). Only 10eyes had zone1 disease. Of the 62 eyes, 72.5 %had more than 6clock hours of involvement. Out of the 62 eyes, 53 eyes had plus disease.

2. Analysis of outcome of laser photocoagulation

In this study screening examination is done at 34weeks or 4 weeks postnatal whichever is earlier. Those infants who are detected to have threshold or pre threshold type AROP were given laser photocoagulation using Laser Indirect Ophthalmoscopic delivery system by ophthalmologists and followed up till retina becomes stable or ROP regresses. Thereafter follow up examinations are performed at 3 months, 6 months and 10 months. Structural outcome was considered unfavourable¹⁵ if there is (1) a posterior retinal fold involving the macula/macular drag (2) a retinal detachment involving the macula, or (3) retrolental tissue or “mass” obscuring the view of the posterior pole. In the

	Category	Frequency	Percentage (%)
Refractive error at 6 months	High myopia	1	1.7 %
	Moderate myopia	8	13.3 %
	Low myopia	24	40.0 %
	Normal	17	28.3 %
	Hypermetropia	10	16.7 %
	Total	60	100.0 %
	Refractive error at 10 months	High myopia	2
Moderate myopia		12	20.0
Low myopia		23	38.3
Normal		15	25.0
Hyper metropia		8	13.3
Total		60	100.0

Table-6: Distribution of Refractive error of study participants at 6 and 10 months (n-60)

Gestational age	Refraction at 6months					Total
	high myopia	Medium myopia	low myopia	normal	hypermetropia	
<28weeks	0	0	2	0	0	2
28-30 weeks	1	2	3	4	1	11
30-32 weeks	0	2	4	2	1	9
32-34 weeks	0	0	3	3	2	8
Total	1	4	12	9	4	30

Table-7: Relationship of Refractive Errors with Gestational Age (n-30)

Factors	Category	Refraction at 6months				Total		χ^2	P value
		Myopia		No Myopia		N	%		
		N	%	N	%				
Gestational age	<30 week	15	57.7	11	42.3	26	100	0.134	0.714
	>30 week	18	52.9	16	47.1				
Birth weight	< 1.5 kg	31	64.6	17	35.4	48	100	8.906	0.003
	>1.5 kg	2	16.7	10	83.3				
Age at diagnosis	<36 week	20	58.8	14	41.2	34	100	0.793	0.373
	>36week	13	50	13	50				

Table-8: Bivariable Analysis of factors associated with Myopia (n-60)

present study the findings are:

Out of the 60 eyes, 54 eyes had a favorable outcome at 3months (Table.3). There was no structural sequel like vessel straightening, retrolental fold, foveal ectopia, macular drag, retinal detachment, retinal thinning or disc pallor. 6 eyes had an unfavorable structural outcome (10 %). All 6 eyes had macular drag. The retinal findings remained stable at 6 months and ten months of follow up in all these infants.

Among the 6 eyes with unfavorable outcome, 4 were of gestational age less than 30 weeks but there was no statistically significant association. Among the studied infants unfavourable outcome occurred in those with birth weight less than 1.5kg. With low birth weight the risk for unfavourable structural outcome is high. Out of the 6 eyes with unfavourable structural outcome, 5 had more than 6 clock hours of involvement. Among the 6 eyes with unfavorable outcome, 4 had stage 3 ROP (Table-4). Unfavourable structural outcome increases with Stage of ROP.

3. Functional outcome measures

The functional outcome was assessed in terms of visual

behavior by assessing the fixation of light, whether child is following light and by preferential looking pattern. The refractive errors were assessed by performing retinoscopy. Other sequels noted were presence of strabismus or nystagmus.

Out of the 30 babies only 1 had an unfavourable visual behavior (Table-5). The baby was not fixing and following light. The baby had global developmental delay and the abnormal visual behavior could be attributed to that since the fundal examination showed a favourable outcome.

4. Refractive Errors

Children are hypermetropic in the first 3 years of life. In full term infants, over the first few years they undergo a process of emmetropisation. But this is disrupted in premature babies and leads to development of refractive errors. Refractive outcome was assessed after cycloplegic retinoscopy. In our study refractive errors have been classified as follows (in terms of the spherical equivalent calculated from the retinoscopy): Hypermetropia: >4D (Diopters), Emmetropia: 0-4D, low myopia 0 to -3D, moderate myopia -3D to -6D, High

myopia $> -6D$ ¹⁶

At 6 months, myopia was the predominant refractive error in the studied group accounting for about 55%. Among the study group 16.7% had hypermetropia. The mean spherical equivalent was 0.23 D (SD 2.92D). The spherical equivalent ranged from -6.5 D to +5.0 D at 6 months. 28.3 % had a normal refractive status (Table-6).

Myopia remained as the predominant refractive error at 10 months of age. The incidence and degree of myopia increased as age advanced. About 61% of the babies had myopia at 10 months of age. 25% had normal refraction. (Table.6) The mean spherical equivalent at 10 months was -0.53 D (SD: 3.24 D; range: -8.0 D to +5.0 D).

The incidence of myopia increased from 55% at 6 months to 61.6% at 10 months. Those with lower degrees of myopia showed a shift to medium to high myopia as age advances.

There is an increase in those with high and medium myopia while the number of hypermetrops was reduced from 16.6% to 13.3 %. Infants with a normal refraction were reduced from 28.3% to 25% (Table-6).

The incidence of refractive error was high in low gestational age group. All babies with gestational age less than 28 weeks had low myopia. As the gestational age increases the number of babies with myopia is decreasing. In 28-30 week age group 54.1% had myopia while it was reduced to 28% in 32-34 age groups (Table-7). Since myopia was the predominant refractive error it was further analyzed:

The incidence of myopia was high among the low gestational age group: as the prematurity increases the chance for myopia increases. 57.7 % of infants with gestational age less than 30 weeks had myopia. It was reduced to 52.9% in more than 32 weeks age group. However the association was not statistically significant.

The incidence of myopia was 64% in less than 1.5kg birth weight group while this was only 16.7% in above 1.5kg birth weight group. That is low birth weight increases the risk of myopia. The association was found to be statistically significant. Early development of ROP is associated with high risk of developing myopia. 61% of infants who were diagnosed to have ROP before 36 weeks of PCA had myopia while the incidence was 50 % in 34 weeks and above (Table-8). 60% of the study participants were found to have astigmatism at 6 and 10 months. That is, there was no worsening of astigmatism as age advances.

DISCUSSION

Retinopathy of prematurity is a disease affecting the retina of premature infants and is characterized by retinal neovascularization¹⁸⁻²⁰. This can result in spectrum of outcomes ranging from the most minimal sequelae without affecting vision in mild cases to bilateral blindness in more advanced cases. Current neonatal practices have improved the survival rate of premature infants; the incidence of ROP is on the rise. Early diagnosis and timely treatment of ROP is very important as it helps to reduce the burden of childhood blindness. The study aims to find out whether early detection and treatment of ROP can improve the structural and

functional outcome in preterm infants which comprises visual function, refractive status and other problems like strabismus, nystagmus. The study was conducted in 31 infants who underwent laser photocoagulation for ROP in Retina clinic RIO Trivandrum during a period of 1 year.

1. Demographic Characteristics: The study population had male female ratio 1:1. No definite gender predilection was noted.

2. Risk factors

A. Gestational age: The mean gestational age of participants was 30.19 weeks (± 1.78 weeks.). This is comparable to a study by Deeksha Katoch, Gaurav Sanghi et al in India¹⁶ (28.99 weeks) and much higher than the ETROP study cohort which had an average gestational age of 25 weeks¹⁵. The incidence and severity of ROP increases with decreasing birth weight and gestational age²¹⁻²³.

B. Birth weight: The average birth weight of infants in the present study was 1240 gm which is much higher than ETROP cohort (705g). This is comparable to 1120 g in the study by Deeksha Katoch, Gaurav Sanghi et al. The rationale for difference in birth weight in Indian scenario is based on the findings by Freider et al ROP is seen in larger babies²⁴. Infants with low birth weight had more chance of unfavorable structural outcome and refractive errors at follow up²⁵⁻²⁸.

3. Disease Characteristics: Out of the 62 eyes, 42 % developed any form of ROP at a post conceptional age of 32-34 weeks. (Table.1) Most of these infants underwent laser treatment around 36-38 weeks (42%). That is 42% of infants developed threshold or pre threshold type I at PCA of 36-38 weeks. This finding is comparable to CRYO ROP study²⁹ in which the mean age of development of threshold disease is 36.9 weeks 37 weeks in ETROP study. Early development of ROP was associated with an increased incidence of myopia.

In our study all babies had ROP in both eyes and it was symmetrical. Out of the 62 eyes 48% had stage 2 and stage 3 disease each (Table.1). Stage 3 disease was more associated with an unfavorable structural outcome. (4 out of 6 eyes with unfavorable outcome had stage 3 disease. 83.9% eyes had zone 2 ROP in the present study and 72.5 % had more than 6 clock hours of involvement. Of the 6 eyes with unfavorable structural outcome 5 were having more than 6 clock hours of involvement.

4. Structural And Functional Outcome: Out of the 60 treated eyes, 90% had a favorable structural outcome at 3, 6 and 10 months. That is the incidence of unfavorable structural outcome is 10% (Table.3). This is comparable to the ETROP study where the incidence of unfavorable structural outcome is 9.1%. In our study all the 6 eyes with unfavorable outcome had macular drag. Although peripheral retinal changes were not seen in our study population the risk for the same persists and hence the need for follow up examinations.

All infants with unfavourable outcome belonged to less than 1.5 kg birth weight group and low birth weight is a

statistically significant predictor of unfavorable structural outcome.(Table 4)

Only 2 out of 30 infants in the present study had strabismus (6.6%) and both had esotropia. This is lower compared to ETROP study which reported strabismus in 22.8%. This low incidence of strabismus may be attributed to short follow up time and bilateral symmetric presentation. Only 1 baby (2 eyes) out of the 30 had an unfavorable visual outcome and had global developmental delay and the abnormal visual behavior could be attributed to this (Table-5).

Myopia was the predominant refractive error in the study group comprising around 55% at 6 months and 61% at 10 months (Table 6). Myopia is a well-known complication of severe ROP.³⁰⁻³¹ The ETROP study had also reported that 80% of threshold ROP infants and 65% of treated high risk pre-threshold infants had myopia. Low birth weight and prematurity contributes to myopia in infancy. In addition to this the incidence of myopia rises in infants with ROP as compared to infants without ROP of same birth weight. Recent studies showed that laser treatment also contributes to myopia in ROP infants.^{32,33} In the present study statistically significant association was found between myopia and low birth weight(Table 7&8). The mean spherical equivalent of the study population was 0.23 D at 6 months and -0.53 at 10 months. That is there is a myopic shift as age advances. This emphasizes the importance of strict follow up in treated ROP infants and also the need for appropriate correction. Also the incidence of astigmatism was very high in the study group (60%).

This study shows that timely early treatment can prevent structural sequel in ROP infants and excellent results comparable to HHDC can be obtained. Also this study stresses that the treatment of ROP must not stop with laser treatment but the need for follow up of these children by treating Ophthalmologist further to manage the forthcoming sequel of refractive errors and others like retinal thinning, retinal hole and detachment.

CONCLUSION

The incidence of favorable structural outcome in our study was 90%. Low gestational age and low birth weights were associated with an unfavourable structural outcome. There is a high prevalence of refractive errors in our study group accounting for about 71.5% at 6 months. The refractive errors increased at 10 month follow up to 77%.Among the refractive errors, myopia predominates accounting 55% at 6 months and 61 %at 10 months. The prevalence of myopia was significantly affected by low birth weight. There was a high prevalence of astigmatism in our study group. Low birth weight, prematurity, ROP and laser contribute to the presence of refractive errors. The incidence of strabismus was 6.6%in our study group.

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