Anatomic and Refractive Outcome After Laser Photocoagulation for Type-1 Prethreshold Retinopathy of Prematurity at a Tertiary Center in Turkey

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ABSTRACT Objective: To evaluate the anatomic and refractive outcomes 1-year after successful laser photocoagulation (LPC) for Type-1 prethreshold retinopathy of prematurity (ROP) at a tertiary center in Turkey. Material and Methods: The study group included infants with Type-1 prethreshold ROP who underwent LPC treatment. The control group included infants who had successfully regressed Type-2 prethreshold ROP without any anatomic sequelae. After 1-year anatomic and refractive outcomes of the eyes were assessed. Results: The study group included 41 infants ([82 eyes; mean gestational age (GA): 28.4±2.03 weeks, mean birth weight (BW): 1115.02±330.88 g]) and the control group included 39 infants (78 eyes; mean GA: 28.5 ± 2.05 weeks; mean BW: 1175±285.56 g). Both groups did not differ significantly in GA, BW and follow-up period (p>0.05). The postconceptional age (PCA) at the time of LPC treatment was 36.10±1.50 weeks. The mean number of laser spots applied per eye was 1184.56±299.31. At the end of corrected 1-year age, refractive error was significantly less myopic in control group (1.95±1.42D) compared to study group (-0.32±2.22D) (p<0.05). Eyes with Zone I ROP were more myopic compared to eyes with Zone II ROP (p<0.01) The prevalence of high myopia was 4.9% in study group. Conclusion: All children in our study did not develop any anatomic sequelae at the end of the study. Risk factors for myopia in Type-1 prethreshold ROP were Zone I involvement and greater number of laser spots.

Key Words: Laser coagulation; retinopathy of prematurity; refraction, ocular; treatment outcome


Anahtar Kelimeler: Lazer koagülasyon; prematüre retinopatisi; refraksiyon, oküler; tedavi sonucu

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Retinopathy of premature (ROP) is a proliferative vascular disorder of the retina and it is a major cause of childhood blindness in developed and developing countries. It affects infants born with early gestational age (GA) and low birth weight (BW).¹

The treatment of the disease has been established in CRYO-ROP (The Cryotherapy for Retinopathy of Prematurity) study and cryotherapy in threshold ROP revealed a rate 44% of unfavorable outcome at the end of 1-year follow-up.² However, subsequent studies reported a higher incidence of unfavorable structural and functional results after treatment of threshold ROP either by cryotherapy or laser photocoagulation (LPC).³⁻⁷

The guidelines for the treatment of the disease have changed after ETROP (Early Treatment for Retinopathy of Prematurity) trial and LPC has become the main treatment modality of ROP. This study identified patients as Type-1 and Type-2 prethreshold ROP and recommended treatment for Type-1 prethreshold ROP that had a high risk of progression. Furthermore, this was the touchstone study displaying better structural and functional outcomes in the management of ROP. Thus, unfavorable functional results showed a reduction from 19.5% to 14.5% and unfavorable structural outcomes were reduced from 15.6% to 9.1%.⁸

Subgroup analysis from ETROP study revealed reduced unfavorable anatomic and functional outcomes with early treatment of Type-1 prethreshold ROP.⁹ But no information exists in the literature about the clinical outcomes after laser treatment for Type-1 prethreshold ROP from our country. Herein, this study demonstrates the anatomic and refractive results of eyes with Type-1 prethreshold ROP after laser treatment during a 1-year follow-up period at a tertiary center in Turkey.

MATERIAL AND METHODS
The study was carried out in Zeynep Kamil Maternity and Children’s Diseases Training and Research Hospital which is one of the largest ROP screening and treatment center in Turkey. A local ethical approval was taken for the study. And the study was concordant to the tenets of the Helsinki Declaration. Several parameters were evaluated including; gestational age (GA) and birth weight (BW) of the neonates, zone and stage of ROP, time of the disease regression, postconceptional age (PCA) at the time of laser treatment, number of laser spots applied for each eye, retinal structural findings and refractive measurements.

A detailed informed consent was obtained from all parents before the laser procedures. A near-confluent laser ablation was performed in all patients with a diode laser device (Iridex; Oculight SL, Mountain View, 810-nm infrared laser, CA, USA) under topical anesthesia by using a 28-D condensing lens. Laser treatments were performed under supervision of a neonatologist and no infant developed any systemic deterioration during treatments. All patients were ordered topical antibiotic and steroid drops for one week postoperatively. The early postoperative follow-up was done at one week. Plus disease disappeared and inactivation of ROP was achieved successfully in all eyes at the end of first week after treatment. There was no per- or post-operative complication seen during the study period.

The follow-up examinations were performed by ophthalmologists experienced in ROP screening and treatment (M.G and G.C). The anatomic and functional outcome of all patients including refractive error, retinal structural sequelae, presence of strabismus, anisometropia or nystagmus were evaluated at 1-year corrected age.

ASSESSMENT OF ANATOMIC AND REFRACTIVE STATUS
A detailed retinal examination was performed in all visits. The presence of retinal anatomic sequelae such as dragging of disc, narrowing of arcades, vitreoretinal membranes, localized tractional tissues or retinal detachment were studied. The follow-up scheme for retinal anatomic evaluation included weekly visits after laser therapy until a complete regression of the neovascularizations and plus disease in study group. Two to three weeks and subsequent monthly visits ensued up to 4 months postnatally until ensuring the clinical stabilization
of the retina. Similar follow-up procedure was executed for the infants in control group who did not require laser treatment.

At corrected 1-year age, all infants were screened for refractive disorders and retinal situation. The refractive statement of the patients were assessed by cycloplegic retinoscopy or automatic refractometry (Welch Allyn; Sure Sight Autorefractor, New York, USA) 30 minutes after instilling 1% cyclopentolate hydrochloride twice with 10 minutes intervals. Spherical equivalent (SE) measurements were used in the present study. The refractive error was classified as myopia (SE ≥-0.25 D) and hyperopia (SE ≥0.25 D). For the design of the current study, high myopia was defined as SE ≥5D and mild to moderate myopia as SE <5D.

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programme was used for the statistical analysis. Descriptive statistical data were given as mean, standard deviation, median, frequency, minimum and maximum. Student t test was used in comparison of normally distributed data and Mann Whitney U test was used to compare nonparametric values. Spearman’s correlation test was performed for the correlation between the two continuous variables. p<0.01 and p<0.05 were both considered statistically significant.

### RESULTS

Totally 80 infants were retrieved for this retrospective study. The study group consist of 82 eyes of 41 infants who had bilateral LPC treatment and the control group included 78 eyes of 39 infants who had successfully regressed Type-2 prethreshold ROP with no need of LPC treatment. The distribution of GA and BW of the infants and the clinical characteristics of the study group were given in Table 1 2. The mean number of laser spots in Zone I ROP was 1686.78±355.51 (1235-2100) and in Zone II ROP was 1064.41±190.19 (800-1520) with statistically significant difference (p<0.01).

The study and control groups did not differ in GA, BW and follow-up period (p>0.05).

| TABLE 1: Distribution of gestational age and birth weight. |
|-----------------|-----------------|-----------------|-----------------|
| Study Group   | Control Group  |
| (n=41)        | (n=39)          |
| Mean±SD       | Mean±SD        |
| Gestational age (weeks) | 28.41±2.03 | 28.05±2.05 |
| Birth weight (g) | 1115.02±330.88 | 1175.49±285.56 |

Study group: Infants with Type-1 prethreshold ROP; Control group: Infants with Type-2 prethreshold ROP.

| TABLE 2: Clinical characteristics of the study group. |
|-----------------|-----------------|-----------------|-----------------|
| Study Group   | Control Group  |
| (n=41 infants (82 eyes) |
| N: 41 infants (82 eyes) |
| Mean PCA at treatment time (weeks) | 36.10±1.50 |
| NLS | 1184.56±299.31 (800-2100) |
| Zone I ROP | 18 eyes (22%) |
| Zone II ROP | 64 eyes (78%) |
| Stage 2 ROP | 3 eyes (3.7%) |
| Stage 3 ROP | 79 eyes (96.3%) |

PCA: Postconceptional age; NLS: number of laser spots; ROP: Retinopathy of prematurity.

No per- or post-operative complications were observed in study group such as anterior segment ischemia or intraocular hemorrhage. All eyes in the study group showed regression of plus disease within 2 weeks after laser treatment. No supplemental LPC sessions were needed. No infants in both groups had unfavorable anatomic outcome at 1-year corrected age.

At 1-year corrected age, refractive error was less myopic in control group (1.95±1.42D SE [median: 2D; range -1D to +5D) compared to study group (-0.32±2.22D SE [median: -0.25D SE; range -6D to +3.5D) with statistically significant difference (p<0.01). In study group, 40 eyes (48.8%) had hyperopia (range between 0.25D to 3.5D SE), 38 eyes (46.3%) had mild to moderate degrees of myopia (range between -0.25D to -4.25D SE) and 4 eyes (4.9%) had higher degrees of myopia (range between -5D to -6D SE). Distribution of refractive error in both groups is shown in Figure 1 and 2.

Eyes with greater number of laser spots were more myopic compared to eyes with lower number of laser spots (p<0.05). Also eyes with Zone I ROP were more myopic compared to eyes with...
Zone II ROP (p<0.01). We did not observe a relationship between the stage of ROP with refractive error (p>0.05) (Table 3).

Two (4.9%) infants had strabismus (esotropia) at 1-year corrected age. These 2 infants developing strabismus had no nystagmus or anisometropia. Other infants in both groups had no anisometropia, strabismus or nystagmus at the end of the study.

DISCUSSION

Ocular structural and functional sequelae of ROP after cryo or laser therapy have been well documented in past literature. Although the cryoablation of the avascular retina was a saver method in its era, higher prevalence of long-term unsatisfactory results have been observed including residual anatomic sequelae, higher degrees of refractive errors, anisometropia, amblyopia, strabismus or nystagmus.10-13 Since subsequent studies have reported better favorable outcomes with LPC treatment, it has replaced cryotherapy as the treatment of the disease worldwide.14,15 After the introduction of ETROP trial, treatment was considered earlier than the threshold level of the disease for Type-1 prethreshold ROP. This study showed improved visual functions in Type-1 prethreshold eyes during early and long-term follow-up periods.16 Also several studies from Turkey reported screening and treatment results of ROP but no information exist about the anatomic and refractive outcome after laser treatment of Type-1 prethreshold ROP.17-22 Therefore, we composed this study to evaluate the clinical outcomes of infants with Type-1 prethreshold ROP after LPC treatment at 1-year corrected age.

Various laser ablation modalities have been described such as additional laser burns to the ridge and vascular retina posterior to the ridge achieving better favorable structural outcomes with a low incidence of additional laser sessions.23-25 In our routine practice, following laser ablation of the whole avascular retina, we perform one to two rows of laser application to the vascular retina posterior to the ridge. We did not observe any laser related complication during our study period. Successful inactivation of the disease was achieved in all cases with no need of any additional laser sessions.

Miscellaneous retinal structural sequelae have been denoted in different reports.24-26 In a study, higher rates of unfavorable anatomic results after laser treatment for threshold ROP was shown such as; peripheral vitreous membranes, disc drag, narrowing of arcades and macular heterotopia.26 We did not observe any peripheral or posterior pole changes during our study period. All eyes had favorable anatomic outcome at the end of 1-year corrected age.

<table>
<thead>
<tr>
<th>TABLE 3: Correlation of default risk factors with refractive error.</th>
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<tbody>
<tr>
<td><strong>Mean refractive error (SE)</strong></td>
</tr>
<tr>
<td>Number of laser spots</td>
</tr>
<tr>
<td>r: -0.480 p: 0.002**</td>
</tr>
<tr>
<td>Zone of involvement</td>
</tr>
<tr>
<td>r: 0.455 p: 0.003*</td>
</tr>
<tr>
<td>Stage of ROP</td>
</tr>
<tr>
<td>r: 0.096 p: 0.550</td>
</tr>
</tbody>
</table>

r: Spearman correlation coefficient *p<0.01; **p<0.05.
ROP: Retinopathy of prematurity; SE: Spherical equivalent.
Several studies reported the refractive results of threshold ROP after LPC treatment. In a study, after performing LPC treatment in 93 eyes, the mean refractive error and the incidence of myopia was observed as -4.71D SE and 80.4% at the end of 1-year follow-up. Algawi et al. showed 40% of myopia in 15 eyes after LPC and 92% of myopia in 25 eyes after cryotherapy. In another study mean refractive error was -2.10D SE in 43 laser treated eyes at the end of 11-years follow-up. Connolly et al. also showed higher degrees of myopia after cryotherapy (mean SE; -7.65D) compared to laser treatment (mean SE; -4.48D) in their cohort of patients. In contrast to these studies, Kiesselbach et al. showed a predominance of hyperopia after laser treatment with an incidence of 14% of myopia. In another study including 28 eyes with Zone I ROP and 60 eyes with Zone II ROP, the mean refractive error was found as -3.80D SE (range between -19D to +4D). Besides, Sahni et al. showed that eyes who underwent treatment either with laser or cryo ablation, were more myopic compared to the eyes who had spontaneously regressed ROP. Also in another study Morrison et al. stated that children with regressed ROP without any structural abnormality had no significant refractive error at early follow-up visits. But 2 years after the initial examination 3.4% of these children developed anisometropia and myopic astigmatism. The authors concluded that children with successfully regressed ROP need close vision screening programmes in their later periods. In our current study, the mean refractive error and the incidence of high myopia were -0.32D SE and 4.9% in laser treated infants. Furthermore, lower degrees of myopia were observed in spontaneously regressed Type-2 prethreshold ROP eyes compared to laser treated Type-1 prethreshold ROP eyes as stated in previous reports.

A study evaluating structural and refractive outcome of Type-1 prethreshold ROP 1-year after laser treatment in Asian-Indian eyes reported a lower degree of refractive error (0.75D SE) than our study. The authors also reported an association between high myopia with greater number of laser spots and greater number of total clock hours of ROP. But the disadvantageous of this study was the lack of a control group in which a meaningful refractive comparison of the laser treated eyes could be provided. In our study, we found higher myopic refractive error in study group compared to control group. And there was a significant relationship of myopia with higher number of laser spots but not with the stage of ROP. Also Zone I involvement of the disease caused higher myopic refraction compared to Zone II involvement of the disease. This means that more posterior location of ROP results in more myopic refraction eventually.

Strabismus, anisometropia and nistagmus have been reported at the end of early and long-term follow-up period after laser treatment for ROP. We did not see any evidence of nystagmus or anisometropia. Nevertheless, we observed strabismus in 2 laser treated infants (4.9%) at the end of the study.

Our results suggested that LPC treatment in Type-1 prethreshold ROP results in better structural and refractive outcome. This was in conformity with previous reports in the literature. Despite successful anatomic outcome during the study period, we reported a total prevalence 51.2% of myopia and 4.9% of strabismus at 1-year age. Hence, these children need to be long-term followed-up in terms of visual and functional outcome.
REFERENCES


