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Myopia, visual acuity and strabismus in the long term following treatment of retinopathy of prematurity

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The purpose of this retrospective study is to evaluate the long-term ophthalmological outcome in children with retinopathy of prematurity (ROP) who were treated for threshold disease with indirect laser photocoagulation. 107 eyes of 56 patients with threshold ROP treated with indirect laser photocoagulation and 202 eyes of 101 control patients with spontaneously regressed ROP were included. Fixation pattern, ocular motility findings, visual acuity, anterior segment examination, cycloplegic refraction and indirect ophthalmoscopic dilated fundus examination findings of all the included subjects were recorded. The incidence of unfavorable visual outcome defined as Snellen acuity of < 0.2, esotropia, strabismus surgery, nystagmus, myopia (≥ -0.50 D) and astigmatism (≥1.50 D) was significantly higher in the treated group than in the control group. These results indicate that premature babies with threshold ROP treated with indirect laser photocoagulation require frequent and long-term follow-up in order to determine refractive status and the presence of ocular motility disorders over time.

***Key words:** retinopathy of prematurity, indirect laser photocoagulation treatment, long-term visual outcome.*

Retinopathy of prematurity (ROP) is a potentially blinding disorder of the immature retinal vasculature of preterm babies, which needs to be detected and treated in a timely and appropriate manner. Although most cases of ROP regress spontaneously, there is a considerable number of patients with threshold disease who need treatment. The main goals of treating threshold disease are to prevent any retinal detachment and to obtain better visual outcome[1]. Many studies have reported unfavorable structural and functional outcome in babies treated for ROP compared to babies with regressed ROP and babies without ROP[2-8]. Although myopia is the most frequent refractive error, children treated for ROP also tend to develop astigmatism, hyperopia, anisometropia and strabismus.

Different treatment methods for ROP have been compared regarding structural and functional outcome. It has been reported in various studies that eyes treated with indirect laser have better anatomic and visual outcomes with less inflammation and fewer systemic and ocular side effects than those receiving cryotherapy. A number of authors suggest that ablative therapy, in particular cryotherapy, contributes to the development of myopia[9-12]. In this study we aimed to assess the long-term visual outcome and motility and refractive status in patients with threshold ROP treated with indirect laser, and to investigate the causes of impaired visual function.

Material and Methods

This retrospective cohort study included 109 eyes of 56 patients with threshold ROP who received transpupillary diode laser photocoagulation treatment. The control group consisted of 202 eyes of 101 subjects with spontaneously regressed ROP. Patients with threshold ROP were either treated in our clinic at Yeditepe University, Department of Ophthalmology, or had received treatment at other hospitals and came to our clinic for follow-up. All subjects had at least two follow-up exams between 2009 and 2013. The findings of the last follow-up visit of each subject were reassessed for this study.

Visual acuity, fixation pattern, ocular motility findings, anterior segment examination, cycloplegic refraction and dilated fundus examination findings were recorded. Visual acuity was determined using a Snellen chart with a “tumbling E” and was expressed with its decimal equivalent. Cycloplegic refraction was carried out in all eyes, either with an autorefractometer (KR-8800) or a handheld autorefractor (Retinomax K- Plus 2), and confirmed with retinoscopy 40 minutes after instillation of cyclopentolate hydrochloride 0.5 % drops, twice at 5-minute intervals. Spherical equivalent refraction (SER) values were used for statistical analysis in all cases. SER ≤ -0.50 D was recorded as myopia, 1.50 D or more cylinder value as astigmatism and SER ≥ +2.00 D as hyperopia. Visual acuity ≥ 0.2 according to Snellen was considered a favorable visual outcome and < 0.2 an unfavorable outcome.

Eyes with tunica vasculosa lentis, cataract or other ocular abnormalities were not included in the study. Three eyes with total retinal detachment, one eye with intravitreal hemorrhage and one eye with phthisis bulbi in the treated group were excluded from the study. Additionally, eyes with aggressive posterior ROP were not included in this study.

Statistical analysis

The data obtained in this study were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 17.0. Descriptive statistical methods (number, percentage, mean, standard deviation) were used to evaluate the data. To determine the difference between the study and control groups, the t-test and chi-square test were used. The findings were evaluated for 95% confidence interval and 5% significance level.

Results

In the treated group (n: 56), mean age at the time of the last follow-up examination was 5.14 (range 3-12), whereas in the control group (n: 101), it was 4.23 (range 3-9). There were 22 males (39.3%) and 34 females (60.7%) in the treated group. The control group consisted of 47 males (46.5%) and 54 females (53.5%).

Birth weight ranged from 650 to 2400 g (mean 1181.9 ±378.4 g) and gestational age at birth from 25 to 33 weeks (mean 28.6 ±2.1 weeks) among the treated patients. In the spontaneously regressed group, birth weight ranged from 750 to 2850 g (mean 1476.7 ±366.5 g) and gestational age at birth from 24 to 36 weeks (mean 30± 2.5 weeks). Both the birth weight and gestational age values were significantly lower in the treated group (p<0.05) (Fig. 1).

In the treated ROP group, due either to insufficient cooperation or to cognitive reasons, the visual acuity data could be obtained from only 45 patients: 53 out of 90 eyes (58.9%) had favorable visual outcomes (Snellen acuity of ≥ 0.2), whereas 37 eyes (41.1%) had unfavorable visual outcomes (Snellen acuity of < 0.2). Among the control group, in which visual acuity data were obtained from 70 patients, only 5% of the eyes had unfavorable visual outcomes while 95% had favorable visual outcomes. The visual outcome differences between the groups were statistically significant according to the t-test (p<0.05) (Table I). Myopia (≤ -0.50 D, mean SE: -5.48 D) was found in 59 eyes (55.1%), astigmatism (≥ 1.50 D, mean 0.45 D) in 51 eyes (47.7%) and hyperopia (≥ +2.00 D, mean SE: +3.53 D) in 12 eyes (11.2%) among the ROP treated group (Fig. 2). In the control group, the incidences of myopia (20 eyes, 9.9%) and astigmatism (27

Table I. Comparison of Visual Acuity Between the Treated and Spontaneously Regressed ROP Groups

		Treated ROP	Spontaneously regressed ROP
Unfavorable VA	Number of eyes	37	7
< 2/10	%	41.1%	5%
Favorable VA	Number of eyes	53	133
≥ 2/10	%	58.9%	95%

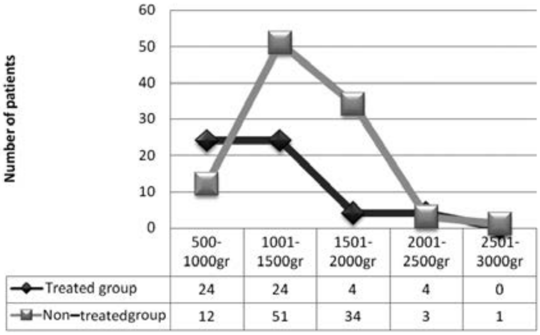

Fig. 1. Birth weights of the treated and the non-treated ROP groups

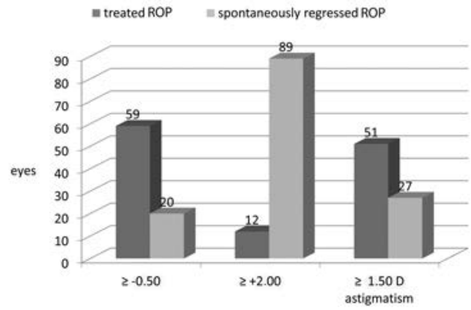

Fig. 2. Comparison of refractive errors between the treated and spontaneously regressed ROP groups

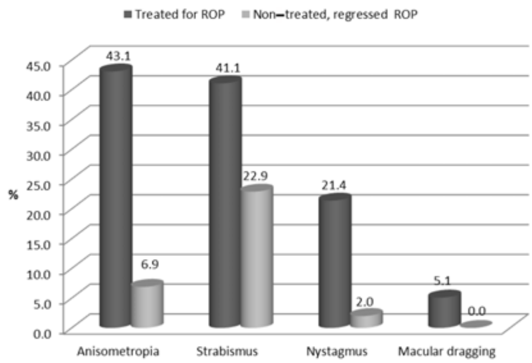

Fig. 3. Comparison of other pathologies in the treated and non-treated groups

eyes, 13.4 %) were lower than in the treated group, whereas the incidence of hyperopia was higher (89 eyes, 44.1%). The differences were statistically significant ($p<0.05$) (Fig. 2). The mean spherical equivalent in the treated group was -2.42 D ±4.43, while it was +1.48 D±2.1 in the control group ($p<0.05$). The rate of anisometropia was significantly lower in the control group ($p<0.05$). It was detected in 22 patients (43.1 %) in the treated group and in only 7 patients (6.9% 9) in the control group (Fig. 3).

In the ROP treated group, 41.1% of the subjects were strabismic: 15 had esotropia (26.8%) and 8 had exotropia (14.3%). In contrast, the total incidence of strabismus was 22.9% in the control group (Fig. 3). In this group, strabismus was diverse: esotropia (11.9%), esoforia (3%), exotropia (4%), esotropia with inferior oblique overaction (IOOA) (2%) and exotropia with IOOA (2%). Four patients (7.1 %) in the treated group were operated on for correction of strabismus. Nystagmus, which was present in 12 subjects (21.4%) in the treated group, was significantly less frequent in the control group (2%) (Fig. 3). Of the 97 eyes in the treated group, 5 eyes developed macular dragging and 2 eyes developed macula-sparing retinal detachment that needed further treatment.

Discussion

Ocular structures develop continuously before and after birth. It is known that premature birth, postnatal stress or disease may affect ocular development and emmetropization[13]. Animal studies have shown that emmetropization is modulated by visual input, resulting in alterations of optical and ocular structures to reduce the refractive error[14,15]. Premature eyes, already having differences in ocular structure compared to the eyes of term babies, may be affected by ROP treatment or regression of ROP, in terms of their refractive development. To evaluate the long-term visual outcome of indirect laser treatment and its effect on emmetropization compared to spontaneous regression, we studied a cohort of children aged between 3 and 12 years who were born prematurely with ROP.

The results of the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study on 247 patients showed that after 10 years, visual deficits were greater in eyes with more severe retinal residua than in eyes with mild or no residua[16]. In view of its relatively less destructive effect on the ocular structures, indirect laser is preferred for the photoablation of avascular peripheral retina in ROP. The American Academy of Ophthalmology has reported that eyes treated with cryotherapy had higher percentages of poor structural and functional outcome than eyes that underwent laser treatment[17]. Various studies comparing cryotherapy to indirect laser photoablation treatment report better structural and visual outcomes with the latter[9-12]. In our study, we reported the outcomes of indirect laser-treated ROP patients, because indirect laser photoablation has increasingly taken the place of cryotherapy in our country.

While myopia is known to be related to the axial length of the eye, it has been reported to be secondary to a shorter anterior chamber, thicker lens and steeper cornea in preterm-born children[13, 18-22]. Although the reason for the increased myopic shift in such babies is not clear, in children who have been treated for ROP it is considered to be the destructive effect of laser rays or cryotherapy on the developing sclera[23-24]. Numerous studies with follow-up durations ranging from 2 to 12 years have reported that prematurely born children who are treated for ROP are more prone to myopia, astigmatism and strabismus compared to those with spontaneously regressed ROP [2-8].

Wang et al.[25] compared treated severe ROP patients with spontaneously regressed or no ROP patients in terms of refractive development and concluded that patients with severe ROP treated with indirect laser photocoagulation progressed rapidly toward myopia, particularly during the first 1.3 years. Anisometropia and astigmatism also increased with age in the treated group. The mild/no ROP group showed little change in refraction.

The mean SER value for the treated group in our study was -5.48 D. Conolly et al.[9] (-4.48D) and Dhawan et al.[26] (-4.71 D) found similar but lower values. In Axer-Siegel et al.'s study[27] 55.2% of the eyes had myopia of ≤ -5.00 D. McLoone et al.[28] and Sahni et al.[29] who investigated smaller groups than ours, reported mild myopic mean SER values. The mean SER was -2.10 D among 43 eyes in the former and -2.40 D among 81 eyes in the latter study.

Unlike children with treated ROP, children with spontaneously regressed ROP and premature children without ROP tend over the long term to develop refractive errors at an incidence similar to that of the general population. In a large series of 1,203 neonate eyes examined in the first week of delivery, preterm babies were found to be myopic, while term babies were mostly hyperopic. It is, however, difficult to state the subsequent refractive status of these babies without long-term follow-up[30-32]. This result may show that the increased incidence of myopia in children treated for ROP could be a result of impaired emmetropization.

Retinopathy of prematurity is known to be a predisposing pathology for strabismus[33]. In our study, we found strabismus in 41.1% (26.8% esotropia and 14.3% exotropia) of the children in the treated group. This was significantly more frequent than in the spontaneously regressed ROP group (22.9%). Although lower rates of strabismus have been reported in various studies, the Early Treatment for Retinopathy of Prematurity (ETROP) study group reported a similar strabismus rate of 42.2% at 6 years among children treated for ROP[3, 6, 31, 34].

Late-onset complications of ROP include strabismus, nystagmus, amblyopia, cataract, glaucoma and retinal detachment. Treated or regressed ROP or prematurity alone are risk factors for late retinal detachments; therefore, it is essential for all prematurely born children—including those without a history of ROP—to be followed up regularly by an ophthalmologist. Three cases of total retinal detachment were detected in our treated group; they were excluded from the study.

Our study has some limitations. Continuity and regularity of follow-up visits were negatively affected by social and economic factors, resulting in a decrease in the number of subjects included in the study. Moreover, even assuming that the more problematic patients had come for follow-up visits, our results might not have reflected the real outcome. A prospective study is necessary for further research to eliminate such limitations. The correlation of myopia and strabismus with gestational age, birth weight, oxygen exposure, and severity and extent of ROP should be studied.

The ETROP study has shown that early treatment of high-risk pre-threshold ROP improves retinal and visual outcomes. These favorable study results have yielded new guidelines for the treatment of infants with ROP. Since the final results of the ETROP study were published, infants with severe ROP have been treated earlier, before fulfilling the threshold criteria, with better structural and functional outcomes[35].

Recently, intravitreal bevacizumab injection has been reported to lead to less myopization and astigmatism compared to indirect laser treatment in infants with ROP at 1 and 5 years of follow-up[36]. Indirect laser photocoagulation, which destroys the peripheral retina and choroid, may in turn impair the normal growth of the retina and support the neovascularization process through inflammation. Therefore, intravitreal antiangiogenic injection seems to be promising, in that it protects the ocular structure and is less invasive. However, it is still too early to determine the systemic or ocular side effects of intravitreal bevacizumab injection. The ongoing Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) and Neonatal Oxygenation Prospective Meta-analysis (NeoPROM) oxygen therapy trials may optimize the current ROP therapy[37].

In conclusion, the majority of patients in our study who were treated for threshold ROP with indirect laser photocoagulation had favorable visual outcomes. However, refractive errors and strabismus incidence were still higher than in spontaneously regressed ROP patients. Therefore, such children need frequent long-term follow-up visits for detection of potential ocular morbidities in a timely manner. Since they will face many social and psychological problems in the future, their families should be aware of the importance of follow-up examinations after treatment for ROP.

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