

# Refractive Status in Children with Laser-Treated Retinopathy of Prematurity: Our Experience in Bulgaria

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## Abstract

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**BACKGROUND:** With the establishment of laser photocoagulation as a standard treatment modality for prethreshold retinopathy of prematurity (ROP), a dramatic reduction of cases with ROP blindness and severe visual impairment have been reported. In the same time, high refractive errors, a common complication in ROP cases and especially in ROP treated infants, have become the main cause of visual and often severe visual impairment.

**AIM:** The purpose of our study was to analyse the long-term refractive status in children at 3.5 years after laser-treatment for type 1 prethreshold ROP.

**PATIENTS AND METHODS:** A retrospective, one centre study of refractive status of 18 children with laser-treated type 1 prethreshold ROP was conducted. The refraction after cycloplegia with 1% cyclopentolate was measured at a mean age of 3.56 years (SD  $\pm$  0.34). Hyperopia was subdivided into two groups – low hyperopia (SE < +5.0 D) and high hyperopia (SE  $\geq$  +5.0 D). Myopia was classified as myopia (SE  $\geq$  -0.25D) and high myopia (SE  $\geq$  -5.0 D). Astigmatism was divided into low astigmatism (plus CD  $\geq$  +1.0 D) and high astigmatism (plus CD  $\geq$  +2.0 D).

**RESULTS:** Thirty-three eyes of 18 children were recruited in the study. Three eyes were excluded because of unfavourable anatomical results. The mean gestational age at birth was 27.3 weeks (24-31 weeks, SD  $\pm$  1.78), and the mean birth weight – 928.9 g (550-1500 g, SD  $\pm$  252.8). The mean spherical equivalent for the whole group was -1.82 D and ranged from -9.00 D to +4.50 D (SD  $\pm$  3.48). Hyperopia was observed in 12 (36.4%) eyes. Myopic refraction had 21 (63.6%) eyes. Astigmatism was detected in 18 (54.5%) eyes. Anisometropia had 3 (16.7%) children. Six children (33.4%) had strabismus (4 esotropia; 2 exotropia).

**CONCLUSION:** High per cent of treated infants for vision-threatening ROP have visual significant refractive errors and strabismus that can cause serious visual impairment if not treated properly and on time.

## Introduction

Retinopathy of prematurity (ROP) is a leading cause of avoidable childhood blindness and severe visual impairment worldwide [1]. Significant advances in neonatology and perinatal medicine in our country in recent years lead to the survival of more and more premature babies born with low and extremely low birth weight, making us contemporaries of the third ROP epidemic. According to the Bulgarian ROP screening guidelines, every prematurely born baby with birth weight (BW) less than 1500 grams and gestational age (GA) below 32 weeks must be screened, and all babies with type 1 prethreshold ROP must be treated preferably with diode laser

photocoagulation [2]. Significant refractive errors and anisometropia are frequently associated findings in ROP patients, especially in treated children [3], [4], [5], [6]. Higher prevalence of high myopia in children treated with cryotherapy for threshold ROP is first discussed in CRYO-ROP study [4]. Later, Early Treatment for Retinopathy of Prematurity (ETROP) study reveals a higher prevalence of refractive errors (myopia, astigmatism) in treated premature babies than in spontaneously regressed ROP infants and mature children, nevertheless better anatomical and functional results in children treated for prethreshold ROP with laser coagulation compared to children treated for threshold ROP with cryoablation or laser therapy [5], [6].

The purpose of our study was to analyze the long-term refractive status in children at 3.5 years after laser-treatment for type 1 prethreshold ROP.

## Patients and Methods

### Patients

A retrospective, one centre study of refractive status of 18 children with laser-treated type 1 prethreshold ROP was conducted. All infants were treated at Pediatric Eye Department, Eye Clinic, University Hospital "Alexandrovska", Medical University, Sofia, Bulgaria for the period August 2011 – December 2013. All children were born prematurely with birth weight less than 1500 grams and gestational age below 32 weeks. Retinal changes before and regularly after treatment were documented with the RetCam imaging system (Clarity Medical Systems Inc., Pleasanton, CA, USA). All children were treated with transpupillary diode laser photocoagulation (Iridex Oculight SLx Tri-Mode 810nm Diode Laser®) by the same qualified pediatric ophthalmologist. The indications for treatment were prethreshold type 1 ROP (zone I, any stage with plus disease; stage 3 ROP in zone I with or without plus disease; stage 3 ROP in zone II with the plus disease) and aggressive posterior ROP (AP-ROP). The laser was applied on the avascular retina without treatment of the present ridge or epiretinal fibrovascular proliferation. Eyes with unfavourable structural outcomes (posterior retinal detachment; retinal fold involving the macula; retrolental fibrous tissue) [4] were excluded from the study.

## Methods

Refraction was measured by cycloplegic retinoscopy with spot retinoscope. A cycloplegia with 1% cyclopentolate and regimen of 3 installations in 15 minutes, and examination in 30 minutes after the third drop was performed. A conversion to the spherical equivalent (SE) was made for every eye for statistic reasons [7].

Hyperopia was subdivided into two groups – low hyperopia (SE < +5.0 D) and high hyperopia (SE ≥ +5.0 D). Myopia and astigmatism were defined using the ETROP trial definitions [5], [6] – myopia (SE ≥ -0,25 D) and high myopia (SE ≥ -5.0 D); astigmatism (plus cylindrical degree (CD) ≥ +1.0 D) and high astigmatism (CD ≥ +2.0 D). Anisometropia was defined as a difference equal or more than 1.0 D for hyperopia and equal or more than 2.0 D for myopia.

The data were analysed using the IBM SPSS 20 software. For statistical purposes of the study, each eye of every infant was used independently.

## Results

Eighteen children, but 33 eyes were conducted in the study. Three eyes were excluded for unfavourable anatomical results – total retinal detachment (1 eye) and retinal folds involving the macula (2 eyes).

The mean age at the time of examination was 3.56 years (range from 3 to 4 years; SD ± 0.34). Sex distribution was almost equal – 10 (55.6%) boys and 8 (44.4%) girls. The mean gestational age at birth was 27.3 weeks (24-31 weeks, SD ± 1.78), and the mean birth weight – 928.9 g (550-1500 g, SD ± 252.8). With extremely low birth weight (under 1000 g) were 13 (72.2%) children and with very low birth weight (1000-1500 g) – 5 (27.8%) children. Zone 2 ROP was observed in 23 (69.7%) eyes; Zone 1 ROP – 5 (15.2%) eyes and AP-ROP – 5 (15.2%) eyes.

**Table 1: BW and GA characteristics in different studies**

Study/author	Year	Mean BW (g)	Mean GA (weeks)
Present study	2017	928.9 ± 252.8	27.3 ± 1.78
Stoica F et al [7]	2016	1363.4 ± 304.7	29.4 ± 1.96
Nguyen PH et al [12]	2015	1426.4	29.8
Katoch D et al [13]	2011	1121.7 ± 254.8	28.9 ± 2.03
Roohipoor R et al [14]	2015	1441 ± 491	28.6 ± 3.2
Axer-Siegel R et al [9]	2008	833 ± 250.3	26 ± 1.9
ETROP [5,6]	2004 <sup>(2011,2013)</sup>	703	25
Yoon JM et al [11]	2017	646 ± 143	24.3 ± 1.1

The mean spherical equivalent for the whole group was -1.82 D and ranged from -9.00 D to +4.50 D (SD 3.48). Hyperopia was observed in 12 (36.4%) eyes – 10 (30.3%) eyes with low hyperopia and 2 (6.1%) eyes with high hyperopia more than +5.00 D SE. Myopic refraction was observed in 21 (63.6%) eyes – myopia in 14 (42.4%) eyes and high myopia in 7 (21.1%) eyes. Astigmatism was observed in 18 (54.5%) eyes.

Low astigmatism was measured in 12 (36.4%) eyes, and 6 (18.2%) eyes had high astigmatism. Anisometropia was observed in 3 (16.7%) children. Six (33.4%) children had strabismus (4 esotropia; 2 exotropia). Three of the strabismic infants were with unfavourable structural results.

**Table 2: Myopia prevalence in different studies**

Study/author	Myopia (%)	High Myopia (%)
Present study	63.6	21.1
Nguyen PH et al [12]	59.0	32.0
Stoica F et al. [7]	70.8	30.2
Axer-Siegel R et al. [9]	55.2	23.9
Katoch D et al. [13]	26.1	1.4
Kaur S et al. [26]	75	26.3
Yang CS et al [25]	77.0	16.7

## Discussion

Bulgaria is a small country in South East Europe with a population of about 7 million people and the delivery rate of 9.2/1000. About 10.0% of all babies are prematurely born with birth weight less than 2500g. Mandatory ROP screening is conducted in almost all neonatal intensive care units of every baby born before 32 gestational weeks and with birth weight less than 1500 g [2], [8]. In different eye centres, different treatment modalities are used – cryotherapy, intravitreal anti-VEGF medications and diode laser photocoagulation [8]. Pediatric Unit of Eye Clinic, University Hospital "Alexandrovska", Department of Ophthalmology, Medical University, Sofia is the biggest centre in Bulgaria and here for a period of 5 years (August 2011 – December 2016) we had 54 children (102 eyes) treated for type 1 prethreshold ROP with diode laser photocoagulation.

According to our ROP guidelines for screening and treatment every prematurely born baby with BW < 1500 grams and GA < 32 weeks must be screened, and if type 1 prethreshold ROP is detected, it must be treated [2]. Different countries have different ROP criteria, according to their social and economic development and neonatal intensive unit care. High-income economies are focused mainly on babies with BW less than 1250 g [5], [9], while other countries have higher criteria – BW < 2000g and/or GA < 34 weeks [7], [10]. In our study, ROP treated children were with a mean birth weight of 928.9 g (SD  $\pm$  252.8g) and meant gestational age of 27.3 weeks (SD  $\pm$  1.78w). They are higher than those reported by studies where ROP screening guidelines were BW < 1250 g [5], [9] and lower than these discussed by many other authors with higher screening criteria [7], [11], [12], [13], [14].

Laser photocoagulation of the avascular retina is the standard treatment modality for ROP and most countries worldwide have been adopted the ETROP study treatment criteria [5] and CRYO-ROP study criteria for unfavourable structural outcomes [4]. In our study we had unfavourable anatomical results in 3 (8.3%) eyes showing the high effectiveness of type 1 prethreshold ROP laser treatment compared to eyes treated at threshold [4], [5], [15].

We had a very high incidence of strabismus (33.4%), but half of the cases were in children with eyes with unfavourable structural results. If we exclude these 3 cases, the strabismus rate just in children with the favourable bilateral outcome will become 20.0%. These results are similar to the squint rate of ETROP study [16] and lower than data reported by Stoica et al., (46.15%) and Sahni et al., (50%) [7], [17]. Very low strabismus rate was found by Katoch et al., (8.3%) and Nguyen et al., (10%) [12], [13]. These big differences between different studies can be mainly explained with the different follow-up time, but all show that esotropia is the main type of

strabismus. In our study, anisometropic amblyopia was the main risk factor for the treatable strabismic cases with our anisometropia prevalence of 16.7%. Nevertheless, this prevalence was very low compared to the results of Stoica et al., with their reported rate of 55.7% [7].

High prevalence of refractive errors, mainly myopia and high myopia are main functional disturbances not only in threshold [15], [18] but in prethreshold ROP laser treated infants [5], [6], [19], [20]. In our study the mean spherical equivalent for the whole group was -1.82 D, which is similar to the results of Kuo et al., (-1.71) [21], Lolas et al., (-1.75 D) [22] and Nguyen et al., (-2.87 D) [12]. Higher SE values than ours were reported in many other studies. Hwang CK et al. reported SE of -5.4 D [23]; Dhawan A et al., had SE of -4.71D [15]; Stoica F et al., found mean SE value of -4.12 D [7].

The most common refraction in our group was myopic. Shortsightedness had 63.6% of the eyes and 21.1% of the eyes were with high myopia more than -5 D. Myopia is very common in children with laser-treated ROP (higher than those that can be found in mature children or premature children with no ROP or spontaneously regressed ROP) and vary significantly from 14% [24] to 77% [25].

In our study hyperopia was observed in 36.4% eyes. Hyperopic rate varies significantly in different studies from 20% [26] to 86% [24], mainly depending on the follow-up duration of the study.

Astigmatism had 54.6% of children, and 18.2% had high astigmatism. Our astigmatic prevalence is similar to that reported by Marinov et al., after 7 years follow-up period – 59.0% [3] and lower than that reported by many authors [7,10] and especially by Yang et al., [25] with their rate of 98% astigmatism rate.

Our study has several limitations. The main limitation is the sample size – 33 eyes of 18 children. The group was small limiting the power of the findings, but have its objective explanations: 1) relatively small number of premature babies and premature babies with ROP that must be treated because of the small population and negative demographic situation in our country; 2) one centre study; 3) the limited infant age of examination – just children between 3 and 4 years. Other limitations of this study are the lack of a control group, short follow-up period and retrospective character.

In conclusion, diode laser photocoagulation is the established treatment modality for prethreshold ROP in Bulgaria in recent years with better anatomical and functional results than cryotherapy [2]. Nevertheless, a high per cent of treated infants have visually significant refractive errors and strabismus that can cause serious visual impairment if not treated properly and on time. This reveals the need for obligatory long-term follow-up examinations of all

prematurely born babies and especially ROP treated infants.

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