

Refractive Error in Patients with Retinopathy of Prematurity after Laser Photocoagulation or Bevacizumab Monotherapy

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Key Words

Retinopathy of prematurity · Laser · Vascular endothelial growth factor · Myopia · Refraction

Abstract

Purpose: To evaluate the refractive development of premature infants with retinopathy of prematurity (ROP) after treatment with laser photocoagulation or intravitreal injection of bevacizumab (IVB). **Methods:** The medical records of patients with ROP treated between 2003 and 2012 who underwent yearly follow-ups were retrospectively reviewed. Patients with residual ROP abnormalities were excluded. The cycloplegic refraction at 3 years of age, assessed using an autorefractometer, was recorded. **Results:** In total, 54 eyes from 54 patients were enrolled. Patients were divided into 4 groups: group 1, including 14 eyes of 14 patients treated with laser therapy; group 2, 15 eyes of 15 patients treated with IVB; group 3, 13 eyes of 13 patients with non-type 1 ROP under conservative follow-up, and group 4, 12 eyes of 12 premature patients without ROP. The mean spherical equivalent at 3 years of age was -1.71 ± 1.27 dpt in group 1, -1.53 ± 2.20 dpt in group 2, 0.63 ± 1.37 dpt in group 3, and 0.41 ± 1.95 dpt in group 4. The mean refractive error differed significantly among the 4 groups ($p < 0.001$). Patients in groups

1 and 2 were more prone to myopia compared with those in groups 3 and 4. Furthermore, patients with type 1 ROP treated by laser photocoagulation (group 1) and those treated by IVB (group 2) had similar refraction ($p = 1$). **Conclusions:** The results of this study suggest that treatment-demanding ROP eyes are susceptible to more severe myopia with age compared with eyes without ROP or those with spontaneously regressed ROP. In addition, the myopic status between laser and IVB treatment did not differ statistically.

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Introduction

Retinopathy of prematurity (ROP) is the most frequent cause of visual impairment in premature infants [1, 2]. ROP is a vision-threatening disease associated with abnormal retinal vascular development at the boundary between the vascular and avascular peripheral retina. Most ROP cases are mild and resolve spontaneously without treatment. However, a small percentage of cases progress to severe ROP, which may cause irreversible vision loss [1, 2]. Reportedly, 26% of treated children with high-risk pre-threshold ROP developed severe visual impairment during the Early Treatment for ROP (ETROP) clinical trial [3].

The effects of several risk factors on the clinical outcomes of ROP have been investigated, including birth history (gestational age and birth weight), postdelivery care (oxygen exposure and infection), and ROP care (screening and treatment) [1, 2, 4, 5]. ROP treatment has now shifted from cryotherapy to laser photocoagulation [3, 6, 7]. Recently, intravitreal injection of anti-vascular endothelial growth factors (VEGFs) was introduced as another therapeutic option [8–11]. With regard to the outcomes of different treatment methods, not only anatomical outcomes but also refractive outcomes should be assessed. Myopia and other refractive errors are among the most common ocular abnormalities associated with premature birth. Several studies reported that the prevalence and severity of myopia is correlated with birth weight, gestational age, and ROP severity [12–14]. Reportedly, eyes with threshold ROP treated by laser photocoagulation exhibited a lower severity of myopia compared with eyes treated by cryotherapy [15–17]. Recently, Harder et al. [18] reported that a single intravitreal injection of bevacizumab (IVB) for the treatment of ROP resulted in less severe myopia and astigmatism at the 1-year follow-up compared with conventional retinal laser coagulation. The BEAT-ROP study group [19] also reported that the severity of myopia at a mean age of 2.5 years was considerably higher in eyes treated by laser treatment (mean, -5.862 dpt/84 eyes without recurrence) than in those treated by IVB (mean, -0.974 dpt/106 eyes without recurrence). However, more data are needed, particularly for the Asian population, to derive adequate conclusions regarding the severity of myopia between ROP eyes treated by laser photocoagulation and those treated by intravitreal injection of anti-VEGFs. Therefore, in this study, we evaluated the refractive development in a cohort of premature Chinese children without ROP, non-type 1 ROP, or type 1 ROP treated by laser photocoagulation or IVB.

Methods

After receiving institutional review board approval, the medical records of ROP patients treated between 2003 and 2012 who underwent yearly follow-ups at Kaohsiung Chang-Gung Memorial Hospital, Taiwan were retrospectively reviewed. Patients with other concurrent retinal abnormalities, residual ROP abnormalities (including macular dragging and retinal detachment), or with irregular or incomplete follow-up examinations were excluded.

The patients were screened for ROP during admission in the pediatric intensive care unit if their birth history included any of the following: a birth weight of $<1,500$ g, birth at a gestational age of <32 weeks, and a birth weight of $>1,500$ g with an unstable clin-

ical course. The patients were first screened at the postnatal age of 4–6 weeks, and follow-up examinations were performed according to the guidelines published by the American Academy of Ophthalmology, American Academy of Pediatrics, and American Association for Pediatric Ophthalmology and Strabismus [20]. The retinal examination findings were classified according to the International Classification of ROP criteria [21]. Laser treatment was recommended between 2003 and 2008 for infants who developed type 1 ROP (group 1), as defined in the ETROP study [7]. Retinal photocoagulation was performed by applying an 810-nm diode laser to produce a gray-white burn of moderate intensity. Spots were applied in a hemiconfluent manner, covering the entire avascular retina from the ridge to the ora serrata. All laser photocoagulation procedures were performed once under general anesthesia by 2 experienced ophthalmologists (H.-K.K. and Y.-H.C.). The mean number of laser spots was 515 ± 130 (range, 361–806; median, 475).

We introduced treatment with off-label IVB in mid-2008 as an alternative to conventional standard laser treatment. Thus, the IVB treatment group (group 2) included patients treated between 2008 and 2011. Informed consent was obtained from the parents of all patients after clearly describing the experimental nature of the IVB treatment. A 0.5-mg (0.02 ml) dose of bevacizumab (Avastin; Genentech Inc., San Francisco, Calif., USA) was injected via the pars plicata after the application of topical anesthesia. The treated eyes were closely monitored, often weekly, until neovascularization regression was detected and the signs of plus disease disappeared. Premature infants with spontaneously regressed ROP (non-type 1 ROP) under conservative follow-up (group 3) and those without ROP who were born between 2007 and 2009 (group 4) were similarly screened. The treated ROP eyes included in this study were treated once by laser photocoagulation or IVB and achieved complete resolution, and those that progressed to stage 4 ROP after treatment were excluded. If the patient received the same treatment in both eyes, the right eye was selected for statistical analysis.

Regardless of treatment, the children were examined yearly after the complete regression of ROP for the fixation pattern, ocular motility, development of the anterior and posterior segments, and refractive status. Refractive errors were measured after 2 years of age. Cycloplegic refraction was evaluated using an autorefractometer (Topcon Kerato-Refractometer 7000, Tokyo, Japan). The spherical equivalent (SEQ) was calculated for all eyes using the following formula: $SEQ = \text{sphere} + \frac{1}{2} \text{cylinder}$. The refractive error at 3 years of age was recorded for all patients. All statistical analyses to compare the SEQ values among the 4 groups were performed using SPSS software (SPSS for Mac, version 22.0; IBM-SPSS Inc., Chicago, Ill., USA). Continuous data are presented as means \pm standard deviations. Significant differences among groups were assessed using ANOVA followed by Bonferroni post-hoc tests. A p value of <0.05 was considered statistically significant.

Results

In total, 54 patients who fulfilled the inclusion and exclusion criteria were enrolled. Groups 1, 2, 3, and 4 included 26 eyes of 14 patients, 27 eyes of 15 patients, 26 eyes of 13 patients, and 24 eyes of 12 patients, respectively. In

Fig. 1. Stages of ROP in the 4 study groups. OD = right eye, OS = left eye. Group 1: ROP with laser therapy. Group 2: ROP with IVB. Group 3: non-type 1 ROP under conservative follow-up. Group 4: premature birth with no ROP. The recorded stage was the most severe stage during the follow-up period for all eyes. In group 2, one eye that progressed to stage 4 after IVB was treated by pars plana vitrectomy and was consequently excluded.

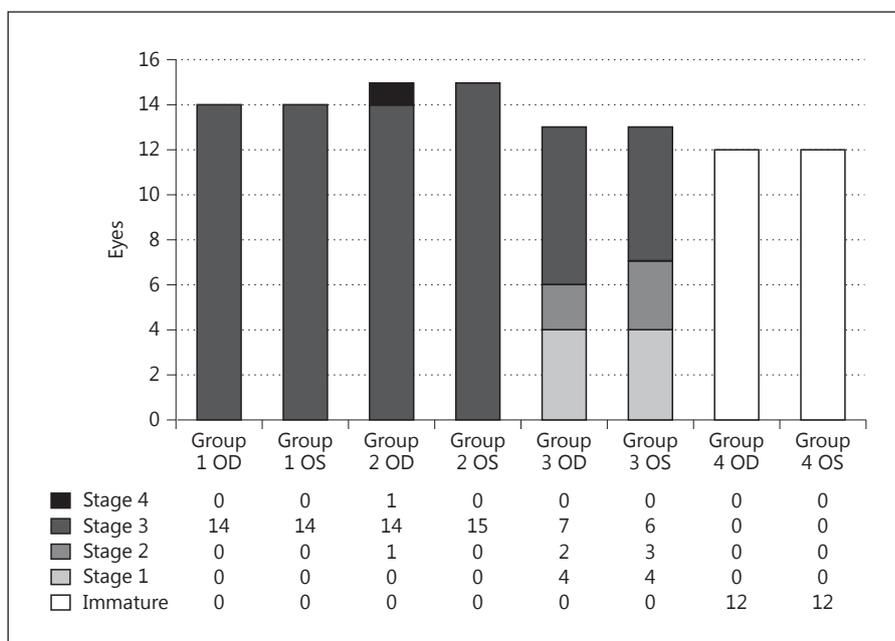


Table 1. Demographic characteristics of the study population

	Group 1 (14 patients)	Group 2 (15 patients)	Group 3 (13 patients)	Group 4 (12 patients)	p value
GA, weeks	27.43±2.93	27.33±2.94	27.69±2.06	29.25±2.90	0.271
BW, g	1,006.79±327.65	1,079.67±357.48	906.15±192.83	1,185.83±250.51	0.121
Gender (F/M)	7/7	8/7	6/7	6/6	0.987

Data are presented as means ± standard deviations or numbers. GA = Gestational age; BW = birth weight; F = female; M = male. Group 1: ROP with laser therapy. Group 2: ROP with IVB. Group 3: non-type 1 ROP under conservative follow-up. Group 4: premature infants without ROP.

group 3, 13 eyes were affected by stage 3 ROP, 5 by stage 2 ROP, and 8 by stage 1 ROP, all of which showed spontaneous regression. The stages of ROP in the 4 study groups are shown in figure 1. Demographic data, including birth weight, gestational age, and sex, are shown in table 1; there were no significant differences among the 4 groups.

Refraction was not significantly different between the right and left eyes (table 2), and the right eyes of all 54 patients were selected for statistical analysis. The mean SEQ at 3 years of age was -1.71 ± 1.27 dpt (range, -4.375 to 0.125 ; median, -1.8125), -1.53 ± 2.20 dpt (range, -5.875 to 1.500 ; median, -1.625), 0.63 ± 1.37 dpt (range, -0.750 to 4.750 ; median, 0.25), and 0.41 ± 1.95 dpt (range, -2.625 to 4.750 ; median, -0.25) in groups 1, 2, 3, and 4,

respectively. None of the eyes exhibited high myopia (>-6.0 dpt). The mean refractive error differed significantly among the 4 groups ($p < 0.001$), and patients in groups 1 and 2 were more susceptible to myopia than those in groups 3 and 4 (table 3). The mean refraction was similar between the group 1 and group 2 patients ($p = 1$) and between the group 3 and group 4 patients ($p = 1$). If data for both eyes were collected to maximize the case number, the mean SEQ was -1.64 ± 1.33 dpt (range, -4.375 to 0.75 ; median, -1.31 ; 26 eyes) in group 1, -1.20 ± 2.20 dpt (range, -5.875 to 4.50 ; median, -1.50 ; 27 eyes) in group 2, 0.58 ± 1.20 dpt (range, -0.875 to 4.75 ; median, 0.25 ; 26 eyes) in group 3, and 0.64 ± 2.00 dpt (range, -2.625 to 5.25 ; median, -0.19 ; 24 eyes) in group 4. Thus,

Table 2. SEQ values among the 4 groups in this study

	Laterality/ treatment (eyes)	SEQ, dpt	P value
Group 1			
Bilaterally treated	OD (12)	-1.73±1.29	0.756
	OS (12)	-1.55±1.46	
Unilaterally treated	Treated (2)	-1.63±1.59	0.186
	Untreated (2)	0.69±0.44	
Group 2			
Bilaterally treated	OD (12)	-1.67±1.69	0.284
	OS (12)	-0.78±2.23	
Unilaterally treated	Treated (2)	1.44±0.88	0.371
	Untreated (2)	-1.80±3.99	
Group 3	OD (13)	0.63±1.37	0.858
	OS (13)	0.54±1.06	
Group 4	OD (12)	0.41±1.95	0.578
	OS (12)	0.88±2.12	

Data are presented as means ± standard deviations or numbers. OD = Right eye; OS = left eye. Group 1: 12 patients were bilaterally treated and 2 patients were unilaterally treated with laser therapy; 2 left eyes were not treated because they exhibited non-type 1 ROP. Group 2: originally, 13 patients were bilaterally treated and 2 patients were unilaterally treated with IVB. However, among the bilaterally treated patients, the right eye of one progressed to stage 4 after treatment and was treated by pars plana vitrectomy. This patient has not been included in this table. Nevertheless, the patient's left eye, which showed regression of ROP after IVB treatment, was still included in group 2 for subsequent statistical analyses. Group 3: non-type 1 ROP under conservative follow-up. Group 4: premature infants without ROP.

the outcomes of the statistical analysis remained mostly unchanged, and there were no significant differences between group 1 and group 2.

Discussion

Several studies have investigated refractive development in premature infants. Chen et al. [14] examined a cohort of children aged 7–9 years who were either born at a gestational age of <35 weeks or had a birth weight of <1,500 g and found a higher prevalence of myopia (48 vs. 29%), hyperopia (23 vs. 15%), and astigmatism (73 vs. 41%) in these children than in age-matched controls. Subgroup analysis showed that eyes with advanced ROP (stage 3 or greater) had more severe myopia and astigmatism. In a longitudinal, prospective controlled cohort

study, Hsieh et al. [22] examined 109 infants, including 74 preterm and 35 full-term infants. Infants with retinal residua of ROP, including macular ectopia and retinal folds, were excluded. At 2 years of age, the mean SEQ was 0.72 ± 0.89 , 0.35 ± 1.05 , 0.38 ± 0.91 , and -1.21 ± 1.85 dpt in full-term infants, preterm infant without ROP, preterm infants with spontaneously regressed ROP, and preterm infants with laser-treated threshold ROP, respectively. Children with laser-treated severe ROP exhibited the highest prevalence of myopia. Wang et al. [23] conducted a similar longitudinal prospective study and found that the prevalence, magnitude, and rate of myopic progression were significantly higher in the severe ROP group treated by laser than in the moderate/no ROP group. Eyes in the severe ROP group progressed rapidly toward myopia, particularly during the first 1.3 years [23]. In the present study, it was also found that severe ROP eyes which received treatment developed myopia more frequently than eyes without ROP or with spontaneously regressed ROP at the age of 3 years.

Previous studies have shown that myopia of prematurity that develops secondary to arrested development of the anterior segment significantly influences the anatomy of optical components, including the development of a steeper corneal curvature, shallower anterior chamber, and thicker lens [14, 23–26]. Most studies have confirmed that ROP severity is a major factor contributing to the refractive error, and cryotherapy was found to induce myopia more frequently than laser photocoagulation in treated threshold ROP eyes [15–17, 26]. However, the difference between laser and intravitreal anti-VEGF injection remains unclear. Several studies have examined the refractive status of treated ROP eyes after laser or anti-VEGF therapy, but direct comparisons are scarce [18, 19, 27]. In the BEAT-ROP report [19], no significant difference was found in the severity of myopia between zone 1 and posterior zone 2 in infants without recurrence, and the mean SEQ was -0.974 dpt in the IVB group and -5.862 dpt in the laser group at the age of 2.5 years. Compared with IVB-treated eyes, a significantly increased prevalence of myopia and very high myopia were identified in the laser-treated eyes. In the study by Harder et al. [18], at the end of a mean follow-up period of 11.4 ± 2.3 months after birth, the refractive error indicated less severe myopia in the IVB group (23 eyes/12 patients; -1.04 ± 4.24 dpt; median, 0) than in the laser group (26 eyes/13 patients; -4.41 ± 5.50 dpt; median, -5.50). However, in the present study, we found that the mean SEQ was -1.20 ± 2.20 dpt (27 eyes/15 patients) in the IVB group and -1.64 ± 1.33 dpt (26 eyes/14 patients)

Table 3. Comparison of SEQ values among the 4 groups included in this study

	SEQ, dpt	95% confidence interval		p value				
		lower limit	upper limit	among the 4 groups	comparison with group 1	comparison with group 2	comparison with group 3	comparison with group 4
Group 1 (14 eyes)	-1.71±1.27	-2.45	-0.98	<0.001	-	1	0.006	0.020
Group 2 (15 eyes)	-1.53±2.20	-2.75	-0.31		1	-	0.012	0.037
Group 3 (13 eyes)	0.63±1.37	0.20	1.45		0.006	0.012	-	1
Group 4 (12 eyes)	0.41±1.95	-0.83	1.64		0.020	0.037	1	-

SEQ values are presented as means ± standard deviations. Group 1: ROP with laser therapy. Group 2: ROP with IVB. Group 3: non-type 1 ROP under conservative follow-up. Group 4: premature infants without ROP. Data were compared among the 4 groups using ANOVA followed by Bonferroni post-hoc tests.

Table 4. Summary of studies measuring the refractive outcomes of laser therapy and IVB for ROP

Author	Publication date	Eyes, n	Gestational age, weeks	Birth weight, g	Treatment	Mean age of examinee, years	Mean SEQ, dpt
Kent et al. [28]	2000	21	25.6±1.6	814±169	Laser	3.4	-2.35
Al-Ghamdi et al. [17]	2004	34	25.5±1.0	747±132	Laser	3.0	-1.80
Sahni et al. [29]	2005	81	26±1.8	862±204	Laser	3.0	-2.40
McLoone et al. [26]	2006	11	26.6±1.7	890±208	Laser	3.0	-0.49
BEAT-ROP [19]	2014	84	24.3*	684*	Laser	2.5	-5.86
Hwang et al. [27]	2015	29	24.8±1.2	701±119	Laser	3.0	-5.3
Current study	2015	26	27.4±2.9	1,007±328	Laser	3.0	-1.64
Martinez-Castellanos et al. [30]	2013	9	NA	NA	IVB	3.0	-1.25
Harder et al. [18]	2013	23	25.2±1.6	622±153	IVB	1.0	-1.04
Chen et al. [31]	2014	40	26.6±1.7	879±213	IVB	2.0	-0.98
BEAT-ROP [19]	2014	106	24.4*	663*	IVB	2.5	-0.97
Hwang et al. [27]	2015	20	24.2±1.0	668±127	IVB	2.0	-2.4
Current study	2015	27	27.3±2.9	1,080±357	IVB	3.0	-1.20

Data for gestational age and birth weight are presented as means ± standard deviations. NA = Not available. * Mean value was calculated from table 1.

in the laser group. This indicated a myopic tendency in the laser group, although the difference was not statistically significant, which may reflect the small sample size in this study.

The mean SEQ of laser-treated ROP eyes at the age of 2–3 years has been reported as -1.80 [17], -0.49 [26], -5.3 [27], -2.35 [28], and -2.40 [29] dpt in previous studies. In the present study, the mean SEQ was -1.64 dpt, while in the BEAT-ROP study [19], the mean SEQ was -5.862 dpt (table 4). Therefore, the severity of myopia was the highest in the BEAT-ROP study. Direct comparisons among these reports are impossible because the

protocols differed with regard to the exclusion of retinal sequelae, which may have influenced the mean values. In addition, gestational age, birth weight, and race varied among studies. However, one important factor influencing refraction is the number of laser spots applied. In the BEAT-ROP study, the mean number was 2,526 ± 1,162 spots in zone 1 and 1,954 ± 1,288 spots in posterior zone 2; the investigators found that myopia increased by -0.14 ± 0.05 dpt for every 100 laser applications, indicating that increased laser ablation induces more severe myopia. In our study, the mean number was 515 ± 130 spots. What remains to be investigated is

whether more aggressive laser ablation is required for the treatment of ROP.

The mean SEQ of IVB-treated ROP eyes at the age of 2–3 years was -1.04 [18], -0.97 [19], -2.4 [27], -1.25 [30], and -0.98 [31] dpt in previous studies. The values were thus similar in these reports and indicated a milder severity of myopia with IVB treatment than with laser treatment. Best-corrected visual acuity values and visual field function survey outcomes were not available for comparison.

In summary, the results of this study suggest that the ROP eyes which required treatment are susceptible to more severe myopia with age compared with eyes without ROP or those with spontaneously regressed ROP. In addition, the mode of treatment may not influence the my-

opic status (laser, -1.64 ± 1.33 dpt; IVB, -1.20 ± 2.20 dpt). The major limitations of our study include the retrospective design and small case population. Despite these limitations, this study provides useful information on the refractive development in Asian premature children with ROP treated by laser or IVB monotherapy. Additional prospective controlled studies are required to determine the more superior of the two treatments (laser and anti-VEGF injection) for ROP.

Disclosure Statement

The authors have no conflicts of interest to declare.

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