



Refractive errors in infants with retinopathy of prematurity treated using laser or anti-vascular endothelial growth factor monotherapy

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ABSTRACT

Background: Infants treated for retinopathy of prematurity (ROP) could develop visually significant refractive errors. In this study, we report pre-treatment refractive errors in premature infants with treatment-requiring ROP treated using laser or anti-VEGF monotherapy and compare the components of post-treatment refractive error values between the two treatment groups at different follow-up timepoints.

Methods: In this retrospective cohort study, we analyzed 360 eyes of 181 premature infants with treatment-requiring ROP who were referred to Farabi Eye Hospital, Tehran, Iran between March 2020 and April 2021. Of the 360 eyes, 195 received laser monotherapy (laser treatment group) and 165 received an intravitreal anti-VEGF injection (anti-VEGF therapy group). All included eyes underwent pre- and post-treatment cycloplegic refraction. Cycloplegia was induced for each infant by instilling a mixed eye drop containing 1% tropicamide, 2.5% phenylephrine, and 0.5% tetracaine (in equal volumes) in each eye three times at five-minute intervals. Cycloplegic refraction was performed 30 minutes after the third instillation.

Results: The mean (standard deviation [SD]) gestational age (GA) and birth weight (BW) of the infants were 29.0 (2.0) weeks and 1241.0 (403.0) g, respectively. The male-to-female ratio in the entire study cohort was 107 (59.1%) / 74 (40.9%), whereas the ratios in the anti-VEGF therapy group and laser treatment group were 47 (56.6%) / 36 (43.4%) and 60 (61.2%) / 38 (38.8%), respectively. The pre-treatment assessment revealed that 218 (60.6%) eyes were hyperopic, 112 (31.1%) were myopic, and 30 (8.3%) were emmetropic. In the anti-VEGF therapy group, 87 (52.7%) eyes were hyperopic, 63 (38.2%) were myopic, and 15 (9.1%) were emmetropic. In the laser treatment group, 131 (67.2%) eyes were hyperopic, 49 (25.1%) were myopic, and 15 (7.7%) were emmetropic. The mean (SD) spherical refractive error and spherical equivalent of refractive error (SEQ) at the 1-week, 1-month, and > 6-month post-treatment follow-up timepoints; the mean cylindrical refractive error at the 3-month post-treatment timepoint; and the mean SEQ at the time of ROP regression were significantly different between the treatment groups (all $P < 0.05$). The rate of anisometropia increased significantly from 3.4% at baseline to 9.2% at the 6-month post-treatment follow-up timepoint ($P < 0.05$).

Conclusions: In this study, the most common pre-treatment refractive status of all included eyes with treatment-requiring ROP and eyes in each treatment group was hyperopia, followed by myopia and emmetropia. At the > 6-month post-treatment follow-up, cycloplegic refraction revealed that the laser-treated eyes were significantly more hyperopic than the anti-VEGF-treated eyes, a finding similar to the pre-treatment refraction results. Further studies of same cohort with a longer follow-up period and a control group are needed to determine the real-world effect of each treatment modality on the refractive statuses of children treated for ROP.

KEYWORDS

infants, neonate, premature infant, prematurity retinopathy, refractive error, laser therapies, intravitreal injection, VEGFs, Avastin

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INTRODUCTION

Retinopathy of prematurity (ROP) is an ocular entity of childhood that is potentially blinding if diagnosed late or left untreated [1, 2]. Its incidence and severity are increasing in developing nations [3]. ROP is responsible for 3 – 11% of all cases of childhood blindness in highly developed countries, and for two-thirds of all cases of childhood blindness in medium-developed countries; however, in low-developed countries, the exact statistics of blindness due to ROP remains unknown [4]. Thus, there is significant interest in ROP screening to facilitate diagnosis in the initial stages of the disease and timely initiation of appropriate interventions for eyes that require treatment [5, 6].

Laser therapy and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection are the two main treatment modalities currently used for the management of treatment-requiring ROP [7]. A cost-effectiveness model revealed that intravitreal anti-VEGF therapy is more economical than laser therapy for the treatment of infants with active or type 1 ROP [8]. However, patients who receive the two treatment modalities show different response rates [7, 9], complication rates [7, 10], and outcomes [10]. In addition, previous studies on some aspects of these two treatment modalities have conflicting results [11].

Furthermore, laser therapy and anti-VEGF may yield different refractive outcomes [12, 13]. Laser monotherapy could cause myopia and high astigmatism [14], whereas anti-VEGF monotherapy is associated with a lower prevalence of myopia or anisometropia compared with laser therapy [15]. Nevertheless, there is no consensus on reduced myopic status with anti-VEGF versus laser treatment [16, 17].

Therefore, the aim of this study was to report pre-treatment refractive errors in premature infants with treatment-requiring ROP treated using laser or anti-VEGF monotherapy and compare the components of post-treatment refractive error values between the two treatment groups at different follow-up timepoints.

METHODS

In this retrospective cohort study, we recruited preterm infants with treatment-requiring ROP who were referred to the outpatient department at Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, between March 2020 and April 2021, and treated using either laser or anti-VEGF monotherapy. The infants were selected using the non-random convenient sampling method. This study was approved by the Board Ethic Committee of Shahid Beheshti University of Medical Sciences (Ethical code: IR.SBMU.RETECH.REC.1399.1364) and conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of all included pre-term infants.

The inclusion criteria were as follows: (1) preterm infants with treatment-requiring ROP treated using laser or anti-VEGF monotherapy; (2) infants who were treated once and did not show relapse; (3) infants with records on pre-treatment cycloplegic refraction; and (4) infants with no congenital or acquired anomalies. We excluded preterm infants who met the following criteria: (1) received additional treatments other than laser therapy and anti-VEGF; (2) had incomplete records; (3) had media opacities or ocular diseases that affect the accuracy of refraction; (4) needed atropine treatment for myopia progression; (5) needed retreatment for ROP; and (6) parents were non-compliant during the course of treatment and the post-treatment follow-up period.

We reviewed 12 000 medical records of preterm infants who visited Farabi Ophthalmology Hospital during the study period, and selected those who required treatment or received treatment and had available data on pre-treatment cycloplegic refraction. A total of 206 infants met the inclusion criteria. Of these, 119 (57.8%) were boys and 87 (42.2%) were girls. Following detailed evaluation, we excluded 25 infants who had optic nerve coloboma ($n = 1$), macular dragging ($n = 3$), a history of vitrectomy ($n = 1$), congenital TORCH infection ($n = 1$), or peripapillary retinal scar ($n = 1$), or underwent more than one treatment session ($n = 18$). Finally, 181 infants, 179 with bilateral ROP and two with unilateral ROP, were included. A total of 360 eyes of the 181 infants were included. Of the included eyes, 195 eyes were treated with laser and 165 eyes with anti-VEGF monotherapy (Figure 1).

Of the 181 included infants, one had a pale optic disc, one had microcephaly, five had hydrocephalus, one had thrombocytopenia, and one received Inderal; all were in the anti-VEGF treatment group. Two infants received platelet injections; one of them was in the laser treatment group and the other in the anti-VEGF group. Three infants in the laser treatment group had a history of blood transfusion. Eleven infants were treated with atropine during follow-up to prevent myopia progression (six were in the anti-VEGF group and five in the laser treatment group), and data on these infants were excluded from the analysis from the time atropine therapy was initiated. Eight of the 181 infants were aged one year old. Only two infants showed different completion times for regression of the vessels in the peripheral retina between the two eyes; therefore, a longer regression time was

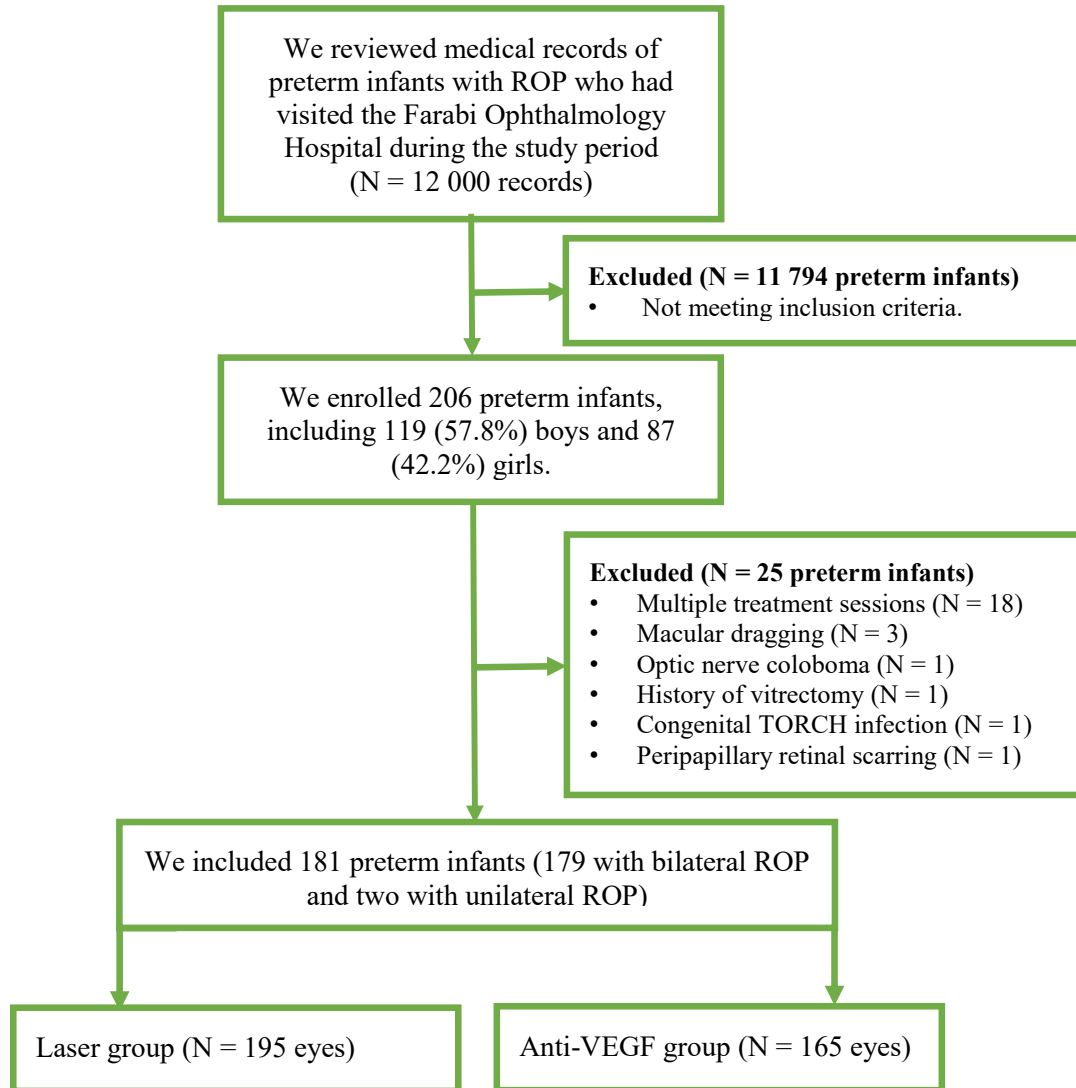


Figure 1. Flow diagram of patient eligibility. Abbreviations: ROP, retinopathy of prematurity; N, number; Laser group, eyes with treatment-requiring ROP treated using laser monotherapy; Anti-VEGF group, eyes with treatment-requiring ROP treated using anti-vascular endothelial growth factor monotherapy.

included in their data for analysis. We considered the corrected age of all the infants [18], and gestational age (GA) and birth weight (BW), as well as the pre-treatment and post-treatment follow-up cycloplegic refraction results, were recorded for all included infants. Regressed ROP was defined as full retinal vascularization (360°) near the ora serrata in anti-VEGF-treated eyes and complete disappearance of ectopic vessels in laser-treated eyes.

All eyes underwent pre-treatment cycloplegic refraction; post-treatment cycloplegic refraction at the 1-week and 1-, 3-, 6-, > 6-month follow-up timepoints, and cycloplegic refraction at time of ROP regression. Cycloplegia was induced for each infant by instilling a mixed eye drop containing 1% tropicamide (Mydrax, Sina Daru Co., Tehran, Iran), 2.5% phenylephrine (Nasophrin 2.5%, Sina Daru Co., Tehran, Iran), and 0.5% tetracaine hydrochloride (Anestocaine, Sina Daru Co., Tehran, Iran) (in equal volumes) in each eye three times at five-minute intervals. Cycloplegic refraction was performed 30 min after the third instillation using a Heine Beta 200 streak retinoscope (HEINE Optotechnik, Herrsching, Germany) in dimly lit room. Cycloplegic refraction for premature infants requires advanced skill and speed because absence of fixed fixation, lack of cooperation, and small pupil size make the procedure challenging. Therefore, an experienced optometrist performed the refraction under the supervision of a senior fellowship-trained retinal specialist and in the presence of the infant's parents or guardians. Each refraction was performed in the same setting and under the same environmental conditions. Refraction results were recorded as the spherical component of the refractive error (sphere) in diopters (D), the

cylindrical component of the refractive error (cylinder) in diopter cylinder (DC) and its axis direction, and the spherical equivalent of the refractive error (SEQ) in D, which was calculated as sphere + 1/2 cylinder. Follow-up examinations were scheduled for each infant based on the observed treatment response.

Intravitreal anti-VEGF (Avastin; Genentech, Inc., South San Francisco, CA, USA) was administered using a 31-gauge needle after instillation of antiseptic drops. The treatment was administered under topical anesthesia at the bedside in an operating room [19, 20]. Laser treatment was administered in the operating room under general anesthesia [20]. Both procedures were performed by a senior fellowship-trained retinal specialist. Details of both treatment procedures are described in a previously published paper from Farabi Eye Hospital [20].

The collected data were analyzed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA). We checked the normality of the data distribution using the Kolmogorov – Smirnov statistic and the normal quantile-quantile plot. The chi-square test, Fisher's exact test, independent sample *t*-test, or the Mann-Whitney U test was used for comparison as appropriate. *P*-value < 0.05 considered statistically significant.

RESULTS

Overall, 181 preterm infants (360 eyes; 179 had binocular ROP and two had monocular ROP) were included in this study. Of these, 107 (59.1%) were male (60 [56.1%] treated with laser therapy and 47 [43.9%] treated with anti-VEGF) and 74 (40.9%) were female (38 [51.4%] treated with laser therapy and 36 [48.6%] treated with anti-VEGF). The mean (SD) GA of all the infants, those in the anti-VEGF therapy group, and those in the laser treatment group was 29.0 (2.0) (range: 24.0 – 34.0) weeks, 28.0 (2.0) (range: 25.0 – 34.0) weeks, and 29.0 (2.0) (range: 24.0 – 34.0) weeks, respectively. The mean (SD) age of their mothers at delivery was 30.0 (6.0) (range: 16.0 – 54.0) years.

Regarding BW, 148 (81.8%), 27 (14.9%), and 6 (3.3%) infants had a BW of \leq 1500 g, 1501 – 2000 g, and > 2000 g, respectively. The mean (SD) BW of all the infants, infants in the anti-VEGF treatment group, and those in the laser treatment group was 1241.0 (403.0) (range: 500.0 – 3500.0) g, 1195.0 (403.0) (range: 500.0 – 3500.0) g, and 1280.0 (401.0) (range: 520.0 – 2570.0) g, respectively.

Tables 1 and 2 show the pre-treatment frequency of refractive errors in each treatment group stratified according to sex (Table 1) and BW (Table 2). Pre-treatment refraction showed that 218 (60.6%) eyes were hyperopic, 112 (31.1%) eyes were myopic, and 30 (8.3%) eyes were emmetropic.

The pre-treatment frequency of refractive errors among the female infants differed significantly between the two treatment groups ($P < 0.001$). Among the female infants, the most frequent refractive error in laser-treated eyes was hyperopia ($n = 56$ eyes, 73.7%), whereas that in anti-VEGF treated eyes was myopia ($n = 31$ eyes, 43.0%). Among the male infants, the pre-treatment frequency of refractive errors was comparable between the two treatment groups ($P > 0.05$) (Table 1).

The pre-treatment frequency of refractive errors among infants with a BW \leq 1500 g differed significantly between the two treatment groups ($P < 0.05$) (Table 2). The most frequent refractive error among infants with a BW \leq 1500 g in both treatment groups was hyperopia ($n = 103$ eyes [67.3%] in the laser-treated eyes and $n = 69$ eyes [48.9%] in the anti-VEGF-treated eyes). However, the pre-treatment frequency of refractive errors among infants with a BW of 1501 – 2000 g or > 2000 g was comparable between the two treatment groups ($P > 0.05$) (Table 2).

Table 1. The pre-treatment frequency of refractive error in eyes with treatment-requiring ROP treated using laser or anti-VEGF monotherapy stratified according to sex

Pre-treatment refractive error	Male infants, n (%), 107 (59.1)		P-value	Female infants, n (%), 74 (40.9)		P-value
	Laser, n (%)	Anti-VEGF, n (%)		Laser, n (%)	Anti-VEGF, n (%)	
Myopia (n = 112 eyes)	33 (27.7)	32 (34.4)	0.274	16 (21.0)	31 (43.0)	< 0.001
Emmetropia (n = 30 eyes)	11 (9.2)	4.0 (4.3)		4.0 (5.3)	11 (15.3)	
Hyperopia (n = 218 eyes)	75 (63.0)	57 (61.3)		56 (73.7)	30 (41.7)	
Total number of eyes in the treatment group	119 (100.0)	93 (100.0)		76 (100)	72 (100)	
Total number of eyes of the male and female infants	212		-	148		-

Abbreviations: ROP, retinopathy of prematurity; n, number; %, percentage. Note: *P*-value < 0.05 is shown in bold; Laser group, eyes with treatment-requiring ROP treated using laser monotherapy; Anti-VEGF group, eyes with treatment-requiring ROP treated using anti-vascular endothelial growth factor monotherapy.

Table 2. The pre-treatment frequency of refractive error in eyes with treatment-requiring ROP treated using laser or anti-VEGF monotherapy stratified according to birth weight

Pre-treatment refractive error	BW ≤ 1500 g		BW 1501 – 2000 g		BW > 2000 g	
	Laser, n (%)	Anti-VEGF, n (%)	Laser, n (%)	Anti-VEGF, n (%)	Laser, n (%)	Anti-VEGF, n (%)
Myopia (n = 112 eyes)	40 (26.1)	57 (40.4)	5 (15.6)	6 (27.3)	4 (40.0)	0 (0.0)
Emmetropia (n = 30 eyes)	10 (6.5)	15 (10.6)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperopia (n = 218 eyes)	103 (67.3)	69 (48.9)	22 (68.8)	16 (72.7)	6 (60.0)	2 (100.0)
P-value	0.006		0.114		0.515	
Total number of eyes in the treatment group	153 (100.0)	141 (100.0)	32 (100.0)	22 (100.0)	10 (100.0)	2 (100.0)
Total number of eyes in the weight group	294		54		12	

Abbreviations: ROP, retinopathy of prematurity; BW, birth weight; g, grams; n, number; %, percentage. Note: P-value < 0.05 is shown in bold; Laser, eyes with treatment-requiring ROP treated using laser monotherapy; Anti-VEGF, eyes with treatment-requiring ROP treated using anti-vascular endothelial growth factor monotherapy.

Table 3. The pre-treatment sphere, cylinder, and SEQ values in eyes with treatment-requiring ROP stratified according to types of refractive error in each treatment group

Refractive error	Sphere (D)			Cylinder (DC)			SEQ (D)		
	Laser	Anti-VEGF	P-value	Laser	Anti-VEGF	P-value	Laser	Anti-VEGF	P-value
Myopia, Mean ± SD	-2.32 ± 1.49	-2.42 ± 1.37	0.720	-0.19 ± 0.65	-0.19 ± 0.46	1.000	-2.42 ± 1.41	-2.52 ± 1.33	0.700
Emmetropia, Mean ± SD	+0.37 ± 0.43	+0.43 ± 0.39	0.690	-0.47 ± 0.69	-0.68 ± 0.59	0.380	+0.13 ± 0.40	+0.09 ± 0.39	0.780
Hyperopia, Mean ± SD	+2.65 ± 1.39	+2.33 ± 1.31	0.090	-0.25 ± 0.61	-0.16 ± 0.34	0.210	+2.52 ± 1.38	+2.25 ± 1.32	0.150
Total, Mean ± SD	+1.23 ± 2.54	+0.34 ± 2.58	0.001	-0.25 ± 0.63	-0.22 ± 0.44	0.610	+1.10 ± 2.52	+0.23 ± 2.28	<0.001

Abbreviations: Sphere, spherical component of refractive error in cycloplegic refraction; Cylinder, cylindrical component of refractive error in cycloplegic refraction; SEQ, spherical equivalent of refractive error in cycloplegic refraction calculated as sphere + 1/2 cylinder; ROP, retinopathy of prematurity; D, diopter; DC, diopter cylinder; SD, standard deviation. Note: P-values < 0.05 are shown in bold; Laser, eyes with treatment-requiring ROP treated using laser monotherapy; Anti-VEGF, eyes with treatment-requiring ROP treated using anti-vascular endothelial growth factor monotherapy.

The mean (SD) pre-treatment sphere, cylinder, and SEQ for all eyes with emmetropia, myopia, and hyperopia in the entire cohort and in each treatment group are shown in Table 3. There were no significant differences in the pre-treatment sphere, cylinder, and SEQ of eyes with hyperopia, myopia, and emmetropia between the two treatment groups (all $P > 0.05$). However, when all the included eyes were considered, the laser-treated eyes were significantly more hyperopic than the anti-VEGF-treated eyes ($P < 0.05$), yet both treatment groups had comparable cylinder ($P > 0.05$) (Table 3).

Table 4 shows mean (SD) sphere, cylinder, and SEQ at baseline and at the post-treatment follow-up timepoints in each treatment group. The mean (SD) sphere and SEQ at the 1-week, 1-month, and > 6-month post-treatment follow-up timepoint and the SEQ at the time of ROP regression were significantly different between both treatment groups (all $P < 0.05$); however, the laser-treated eyes were significantly more hyperopic at these follow-up points than the anti-VEGF-treated eyes. Except at the 3-month post-treatment follow-up timepoint ($P < 0.05$), both treatment groups had comparable cylinder at all post-treatment follow-up points (Table 4). The rate of anisometropia in all treated eyes increased significantly from 3.4% at baseline to 9.2% at the 6-month post-treatment follow-up timepoint ($P < 0.05$).

DISCUSSION

In this retrospective cohort study of 360 eyes of 181 premature infants with a mean GA and BW of 29.0 weeks and 1241.0 g, respectively, the most common refractive status in the entire cohort and in each treatment group was hyperopia, followed by myopia and emmetropia. There were no significant differences in the baseline sphere

Table 4. The mean baseline and post-treatment sphere, cylinder, and SEQ values in each treatment group measured using cycloplegic refraction

Time point	Sphere (D)			Cylinder (DC)			SEQ (D)		
	Laser	Anti-VEGF	P	Laser	Anti-VEGF	P	Laser	Anti-VEGF	P
Pre-treatment, Mean ± SD	+1.23 ± 2.54	+0.34 ± 2.58	0.001	-0.25 ± 0.63	-0.22 ± 0.44	0.610	+1.10 ± 2.52	+0.23 ± 2.58	0.001
1 week post-treatment, Mean ± SD	+1.78 ± 2.31	+0.004 ± 1.87	<0.001	-0.36 ± 0.49	-0.28 ± 0.46	0.298	+1.61 ± 2.30	-0.13 ± 1.79	<0.001
1 month post-treatment, Mean ± SD	+2.84 ± 2.15	+1.69 ± 2.41	0.002	-0.38 ± 0.50	-0.44 ± 0.55	0.593	+2.65 ± 2.14	+1.47 ± 2.30	0.001
3 months post-treatment, Mean ± SD	+2.85 ± 1.69	+3.06 ± 1.85	0.348	-0.84 ± 0.86	-0.42 ± 0.54	0.003	+2.44 ± 1.75	+2.83 ± 1.83	0.096
6 months post-treatment, Mean ± SD	+2.05 ± 1.39	+1.80 ± 2.69	0.446	-1.11 ± 0.72	-0.89 ± 0.68	0.061	+1.49 ± 1.51	+1.36 ± 2.73	0.312
ROP regression, Mean ± SD	+2.63 ± 1.87	+1.42 ± 2.63	0.003	-0.52 ± 0.60	-0.65 ± 0.57	0.118	+2.37 ± 1.94	+1.10 ± 2.63	0.003
> 6-months post-treatment, Mean ± SD	+1.71 ± 2.23	+1.03 ± 2.44	0.035	-0.62 ± 0.63	-0.62 ± 0.60	0.751	+1.39 ± 2.35	+0.73 ± 2.43	0.028

Abbreviations: Sphere, the spherical component of refractive error in cycloplegic refraction; Cylinder, the cylindrical component of refractive error in cycloplegic refraction; SEQ, the spherical equivalent of the refractive error which was calculated as sphere + 1/2 cylinder; ROP, retinopathy of prematurity; D, diopter; DC, diopter cylinder; P, P-value; SD, standard deviation. Note: P, P-values < 0.05 are shown in bold; P, the P indicates significant difference in the components of refractive error values between treatment groups at different timepoints; ROP regression, full retinal vascularization (360°) near the ora serrata in anti-VEGF-treated eyes and complete disappearance of ectopic vessels in laser-treated eyes; Laser, eyes with treatment-requiring ROP treated using laser monotherapy; Anti-VEGF, eyes with treatment-requiring ROP treated using anti-vascular endothelial growth factor monotherapy.

or SEQ of eyes with hyperopia, myopia, and emmetropia between the two treatment groups; however, when all the included eyes were considered, laser-treated eyes were significantly more hyperopic than anti-VEGF-treated eyes and remained significantly more hyperopic at the > 6-month follow-up examination, which was the final follow-up timepoint. In addition, we noted a significant increase in the rate of anisometropia from baseline to 6-months post-treatment in all treated eyes.

Simmons et al. [15] enrolled the right eyes of 48 extremely preterm infants with a BW of < 1000 g and a GA of 23 – 27 weeks (22 infants in the intravitreal bevacizumab [IVB] group and 26 in the laser group). Baseline refractive error was comparable between the two groups; however, the laser-treated eyes showed a significantly more myopic shift at the final follow-up visit than the IVB-treated eyes. In addition, although the authors observed a significant increase in anisometropia in the two groups before the age of 1.1 years, the prevalence of anisometropia at the final visit was not significantly different between the groups [15]. Lee et al. observed significantly less myopia in anti-VEGF-treated eyes than in laser-treated or combined laser and IVB-treated eyes [21]. In the present study, most of the included infants had a low BW (148 [81.8%], 27 [14.9%], and 6 [3.3%] of the infants had a BW of ≤ 1500 g, 1501 - 2000 g, and > 2000 g, respectively). The baseline mean SEQ of the laser-treated eyes was significantly more hyperopic than that of the anti-VEGF-treated eyes and remained significantly more hyperopic at the final > 6-month follow-up visit. However, Kue et al. observed a comparable myopic status between anti-VEGF- and laser-treated eyes with ROP at three years of age [16]. This may indicate a possibility that these differences between anti-VEGF- and laser-treated eyes with ROP resolve after a long follow-up period. Thus, a study of the same cohort of infants with a longer follow-up period is required to determine the long-term effects of both treatment modalities on the refractive statuses of eyes with treatment-requiring ROP.

Roohipoor et al. [20] reviewed data from 986 eyes of 493 premature infants with ROP who received laser or anti-VEGF therapy and were followed up for more than 12 months. They observed significantly higher sphere and SEQ values in laser treated-eyes (mean [SD]: - 1.31 [2.83] D and - 2.84 [2.77] D, respectively) than in anti-VEGF-treated eyes (mean [SD]: 0.19 [3.21] D and - 1.26 [3.19] D, respectively), but no significant difference in the astigmatic powers of the eyes in both groups [20]. Harder et al. [13] analyzed 49 eyes with ROP and found that at the end of a 1-year follow-up period, eyes treated with anti-VEGF were significantly less myopic than the laser-treated eyes (mean [SD]: - 1.04 [4.24] D and - 4.41 [5.50] D, respectively). The mean (SD) refractive astigmatism in the anti-VEGF-treated eyes (- 1.0 [1.04] D) was significantly lower than that in laser-treated eyes (1.82 [1.41] D) [13]. In the present study, we observed that the laser- and anti-VEGF-treated eyes had comparable mean (SD) cylinder powers at 6 months (- 1.11 [0.72] DC versus - 0.89 [0.68] DC), at the time of ROP regression (- 0.52 [0.60] DC versus - 0.65 [0.57] DC), and at the > 6-month post-treatment follow-up timepoint (- 0.62 [0.63] DC versus - 0.62 [0.60] DC). The two treatment groups had comparable cylinder values at baseline as well. However, in contrast to the results of the abovementioned previous studies, the sphere and SEQ values of the laser-treated eyes in the present study were significantly more hyperopic than those of the anti-VEGF-treated eyes at the final visit, a finding that is similar to the baseline cycloplegic refraction results. This discrepancy may be attributed to the differences between the follow-up durations of the previous studies and the present study or observed differences between treatment groups at baseline examination.

Kabatas et al. [22] investigated 108 eyes of 54 children with ROP who were treated with laser (n=36 patients) or anti-VEGF (n=18 patients). The mean (SD) GA and BW in the bevacizumab monotherapy, ranibizumab monotherapy, and laser treatment groups were 26.1 (2.27) weeks and 841 (235) g, 26 (1.26) weeks and 840 (177) g, and 27.7 (2.7) weeks and 1112 (362) g, respectively. At 18 months, the mean (SD) SEQ in the bevacizumab monotherapy-, ranibizumab monotherapy-, and laser-treated eyes was - 1.49 (3.04) D, - 1.79 (2.87) D, and - 1.27 (2.80) D, respectively, which were comparable. The authors also reported a comparable magnitude of astigmatism among the treatment groups [22]. Similarly, in the present study, the magnitude of astigmatism at the final follow-up examination was not significantly different between the treatment groups; however, the mean sphere and SEQ of the laser-treated eyes was less myopic than that of the anti-VEGF-treated eyes. This difference may also be attributed to the difference in follow-up periods between these two studies. However, it should be noted that in the present study, all eyes in the laser treatment group were significantly more hyperopic at baseline than those in the anti-VEGF therapy group; however, both groups had comparable cylinder values.

Gunay et al. [23] analyzed 76 eyes of 42 infants with ROP with an adjusted age of 1 year. The median (Q_1 , Q_3) GA and BW of the infants in the bevacizumab monotherapy and laser treatment groups were 26 (25, 27) weeks and 802.5 (660, 970) g, and 28 (26.5, 29) weeks and 925 (850, 1092.5) g, respectively. They found no significant differences in SEQ between anti-VEGF-treated eyes, laser-treated eyes, and eyes with spontaneously regressed ROP (median [Q_1 , Q_3] SEQ: 0.25 [- 1.50, 2.50] D, 0.75 [- 0.87, 1.88] D, and 0.75 [0.25, 1.82], respectively) [23]. Similarly, Mueller et al. [9] analyzed 108 eyes of 54 infants and at the 12-month follow-up, they found no significant difference in SEQ between anti-VEGF- and laser-treated eyes with posterior ROP [9]. In the present study, the mean (SD) SEQ of laser- and anti-VEGF treated eyes was not significantly different at the 6-month post-treatment visit (+ 1.49 [1.51] versus + 1.36 [2.73]); however, the SEQ of laser-treated eyes was significantly more hyperopic than that of anti-VEGF-treated eyes at the time of ROP regression (+ 2.37 [1.94] versus + 1.10 [2.63]) and at the > 6-month post-treatment visit (+ 1.39 [2.35] versus + 0.73 [2.43]).

Roohipoor et al. [24] evaluated 232 eyes of 116 infants with ROP randomly allocated to an anti-VEGF or laser treatment group. The mean (SD) GA and BW of the infants in the anti-VEGF therapy and laser treatment groups were 28.75 (1.86) weeks and 1232 (3180) g, and 28.32 (2.11) weeks and 1273 (273) g, respectively. The authors found no significant difference in spherical and cylindrical refractive errors at a postmenstrual age of 22.5 months [24]. In the present study, we included infants from the same hospital and observed no significant difference in the magnitude of astigmatism between the two treatment groups at the final follow-up; however, sphere and SEQ values differed significantly between the two treatment groups at the > 6-month post-treatment follow-up. The difference in results may be due to the shorter follow-up period in the present study. Thus, a longer follow-up observation of same cohort is required to verify this finding.

A strength of this study is that we excluded infants with incomplete records and double-checked the data of all included infants. An experienced optometrist performed the cycloplegic refractions for all the included infants under the supervision of a senior fellowship-trained retinal specialist. Moreover, we excluded infants who required atropine therapy to prevent the progression of myopia. The infants were excluded from the time the therapy was initiated because atropine therapy could affect the observed changes in refractive error. This study had some limitations. First, the examination time was long (an average of 20 minutes for the initial examination

and a waiting time of 20 - 30 minutes for the onset of cycloplegia), which caused fatigue and restlessness in infants. In addition, performing the cycloplegic refraction required advanced skill and patience. Second, some parents visited the clinic irregularly due to the coronavirus disease pandemic, and several infants were lost to follow-up. Considering the differences in the numbers of infants in the refractive status subgroups, this study should be replicated using a larger sample size and a more homogenous number of infants in each subgroup. We recommend continuing this study by contacting parents or guardians of included infants and performing cycloplegic refractions at several follow-up points after the end of the coronavirus disease pandemic. The final robust conclusions should be made after a long follow-up period. In the present study, 11 infants received atropine therapy during follow-up to prevent the progression of myopia. Considering that the number of infants that showed myopia progression in both treatment groups was almost equal, the possible causes that played a role in the development of myopia in both treatment groups in this cohort need to be studied in the future.

CONCLUSIONS

In this study, the most frequent pre-treatment refractive status among all included eyes with treatment-requiring ROP and those in the laser and anti-VEGF treatment groups was hyperopia, followed by myopia and emmetropia. At the > 6-month post-treatment visit, cycloplegic refraction revealed that the laser-treated eyes were significantly more hyperopic than the anti-VEGF-treated eyes, despite both groups having comparable SEQs at the 6-month post-treatment follow up visit. Further studies of same cohort with a longer follow-up period and a control group are strongly recommended to determine the real-world effect of each treatment modality on the refractive statuses of children with treatment-requiring ROP.

ETHICAL DECLARATIONS

Ethical approval: The study was approved by the Board Ethic Committee of Shahid Beheshti University of Medical Sciences (Ethical code: IR.SBMU.RETECH.REC.1399.1364) and conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of all included pre-term infants.

Conflict of interests: None

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