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Refractive outcome of intravitreal bevacizumab injection in comparison to spontaneous regression of retinopathy of prematurity (ROP)

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ABSTRACT

Purpose: To assess refractive errors in preterm infants following intravitreal bevacizumab (IVB) injection for retinopathy of prematurity (ROP) and to compare it with premature babies with spontaneous regressed ROP.

Materials and Methods: Eighty seven premature infants were included in this study, comprising group1: 38 infants who underwent IVB monotherapy, and group2: 49 infants with spontaneously regressed ROP. Cycloplegic refraction was performed for all infants at 1-year adjusted age and the refractive outcome was compared between the groups.

Results: At 1- year adjusted age, the mean SEQ value was not significantly different between group 1 and 2 (p = .646). Four eyes (10.5%) in group1 and 4 eyes (8.2%) in group 2 were myopic. Also, refractive anisometropia was found in 9 infants (23.7%) from group1 and 5 infants (10.2%) in groups 2, which was not significantly different between groups (χ^2 (1, n = 87) = 2.87, p = .081). At the time of follow up, none of our cases were strabismic. After making an adjustment for gestational age and birth weight in a logistic regression model, mean SEQ was not significantly different between two groups (p = .61)

Conclusion: At adjusted 1 year of age, refractive outcomes were not significantly different between premature infants who underwent IVB injection and the infants with spontaneous regression of ROP. Further studies with longer duration are warranted to elucidate the effects of IVB on the emmetropization process. Biometry assessments would be helpful in this regard.

Introduction

Retinopathy of Prematurity (ROP) is a retinal vascular proliferation in premature infants. It is one of the leading causes of vision impairment in children, and in developing countries, it is believed to be responsible for 6-18% of childhood blindness.¹ The prevalence of ROP in Iran has been reported to be 26.1%.² In the city of Mashhad, the prevalence of ROP in premature infants with a gestational age of less than 32 weeks and birth weight of less than 1500 g, was estimated to be 26.2%, indicating a relatively high prevalence of this disorder in our country.³ Refractive problems such as myopia, astigmatism, and anisometropia are common in preterm infants.⁴ In recent years, there have been promising results of the use of anti-vascular endothelial growth factor (VEGF) drugs, especially bevacizumab. Less refractive errors have been reported when using intravitreal bevacizumab (IVB) injection in comparison with laser therapy.⁵ In spite of identified complications from panretinal photocoagulation, such as the destruction of a significant portion of the retina, decreased

visual field and myopia progression, this method has been used for the treatment of ROP in the last two decades. Although the results of studies on the treatment of ROP using bevacizumab injection, are promising, further investigation is needed in this regard.⁶

Previous reports have suggested that ROP is associated with the development of myopia.^{7–9} On the other hand, it is believed that ROP associated myopia is multifactorial and can vary depending on the prematurity, severity of ROP, and the treatment itself for ROP (whether laser or anti-VEGF).⁷ For example, studies have shown that laser therapy can lead to greater myopic progression than IVB treatment.¹⁰

Possible complications, financial costs, and most importantly the irreversible effects of not choosing an effective treating method on the quality of vision of infants with ROP, suggest the need for further studies in this area. Comparing refractive alongside other outcomes of the various treatment modalities can determine superior treatment in these regards.

Studies have been done to compare refractive errors in preterm and full-term infants or to compare therapeutic

KEYWORDS

Premature infant; retinopathy of prematurity (ROP); intravitreal bevacizumab injection (IVB); refractive error options such as laser therapy and anti-VEGF injection, or comparison of infants with and without ROP. But, in literature, there is less information about the refractive results of IVB injection in premature neonates with ROP, in comparison with infants with spontaneous regression of ROP. In this study, we aimed to provide more knowledge in this field by comparing these groups of patients.

Materials and methods

After obtaining parental informed consent (which covered permission for involving in the study, performing refraction and using the data with confidentiality) and ethical consent form ethical board of our institution and considering the ethics of the Declaration of Helsinki, a total of 87 infants (174 eyes) were enrolled in this prospective study, between September 2017–February 2019. Premature infants with gestational age (GA) of less than 30 weeks and birth weight (BW) less than 1500 g, were included. Patients were categorized into two groups. group1: infants who underwent IVB monotherapy according to BEAT ROP group recommendations,¹⁰ and group2: premature infants with spontaneously regressed ROP who had no anatomical sequelae.

Screening and follow-up examinations and the termination of screening examinations were according to the recommendations of the American Academy of Ophthalmology, American Academy of Pediatrics and American Association for Pediatric Ophthalmology and Strabismus.¹¹

Retinal assessment

After obtaining pupillary dilation and topical anesthesia, the retinal examination was performed for each infant, using binocular indirect ophthalmoscope with +28 D condensing lens, and RetCam (Clarity medical systems, Pleasanton, CA, USA) for image documentation. Scleral depression was performed as needed. To confirm the accuracy of zone diagnosis, the images were reviewed by two ophthalmologists.

IVB injection

First, a lid speculum was inserted in the eye. After topical anesthesia with three drops 0.5% Tetracaine and administration of 10% povidone antiseptic solution to the ocular surface, 0.625 mg bevacizumab (Avastin[®], Roche, Basel, Switzerland) was given into the vitreous with a 31-gauge needle. The injection was applied 1 mm behind the limbus and through the pars plicata. A weekly follow up was considered to ensure about the need for additional treatment.¹¹

Refractive error assessment

Thirty minutes after instillation of three drops tropicamide 1%, separated by 10-min intervals, refraction was assessed using retinoscopy. In order to find consistency between measurements, refraction findings were doublechecked by 2win handheld auto refractometer (2win, Adaptica co., Italy). Refraction was obtained at almost 1-year-old corrected age which was defined as: 52 weeks+ number of weeks the infant was born before 40 weeks (40 weeks were considered as term age). Spherical equivalent (SEQ) more than 1 D between two eyes was considered as anisometropia and SEQ>-5.00D defined as high myopia. Myopia was defined as SEQ ≤ -0.25 .^{12,13}

Statistical analysis

Data analysis was performed using SPSS statistical software for windows, version 16 (SPSS, Inc. Chicago, IL). Kolmogorov–Smirnov test was used to assess the normal distribution of variables. In the case of normal distribution of variables, the Chi-square test was used to compare qualitative variables and χ and p values were reported. Paired and independent samples t-tests were performed for comparison between two eyes and two groups, respectively. Also, the Pearson test was used to assess any correlation between quantitative variables. A logistic regression model was made to find the effect of GA and BW on refractive error findings. For all tests, p < .05 was set as significant.

Results

At the end of the study, the records of 87 infants (174 eyes) were evaluated. Table 1 shows the baseline characteristics of participants in two groups. Group 1 consisted of 38 infants (76 eyes) with type 1 ROP: 10 (26.3%) with zone I and 28 (73.7%) with zone II posterior. Group 2 consisted of 49 infants (98 eyes) with type 2 ROP (2 infants (4.1%) with zone I, 32 (65.3%) with zone II ROP, and 15 cases (30.6%) had zone III ROP at the time of admission) which was spontaneously regressed with no anatomical sequelae at 1 year adjusted age. Stages of ROP in each group have been presented in Table 1. Infants in two groups were significantly different for the ROP zone and stage ($\chi(1)$ = 19.52, p < .001, and $\chi(1) = 12.89$, p = .002, respectively). GA and BW were significantly lower in group 1 (Table 1). Also, two groups were not significantly different regarding gender (χ^2 (1) = 0.397, *p* = .343).

According to our findings, right and left eyes of patients were not significantly different for SEQ and astigmatism magnitudes (t (172) = -0.24, p = .81; and t (172) = -0.449, p = .654, respectively). (Table 2).

Table 1. Baseline clinical characteristics of the infants in two groups.

		Group1	Group2	t-value	p- value
Study group (n)		38 (43.7%)	49 (56.3%)		
Birth weight (grams)		916.47 ± 93.62	1270.2 ± 110.65	-15.71	<.001
Gestational age (weeks)		26.89 ± 0.95	29.10 ± 0.98	-10.52	<.001
5		(25–28 weeks)	(27-30 weeks)		
Chronological age at the time of refraction (weeks)		65.02 ± 0.82	63.04 ± 1.10	9.30	<.001
Gender	Males	25 (65.8%)	29 (59.2%)	X ² -value	.343
	Females	13 (34.2%)	20 (40.8%)	0.397	
ROP Zone	I	10(26.3%)	2(4.1%)	19.52	<.001
	II	28(73.7%)	32(65.3%)		
		-	15(30.6%)		
ROP Stage	1	14(36.8%)	30(61.2%)	12.89	.002
	2	16(42.1%)	19(38.8)		
	3	8(21.1%)	-		

Because of the high correlation between right and left eye, findings from the right eye of the patients were included in statistical analysis.

At 1 year adjusted age, the mean SEQ value was $+1.26 \pm$ 0.86 D (range: -0.50 D to +3.00 D) in group 1, and $+1.37 \pm$ 1.14 D (range: -1.88 D to +5.00 D) in group 2. Mean SEQ was not significantly different between groups (t(85) = -0.461, p = .646), also mean astigmatism was not significantly different between groups (t(85) = -1.53, p = .131). (Table 3) In group 1, astigmatism magnitude was 0.63 \pm 0.67 D (range: 0.00 to 2.00 D), and the axis was between 0 and 20 degrees. Two eyes showed oblique astigmatism (axis 45 and 135 degrees). In group2: mean astigmatism magnitude was 0.42 ± 0.62 D (range: 0.00 to 2.25 D), and the axis was between 0 and 20 degrees. Oblique astigmatism was found in one eye (axis 135 degrees). In group 1, Pearson correlation analysis showed no significant correlation between gestational age (GA) and SEQ (r = -0.129, p =.441), but the birth weight (BW) and SEQ value at 1-year adjusted age were significantly correlated (r = -0.331 and p = .041). In group 2, no statistically significant correlation was found between gestational age and SEQ (r = -0.088, p =.548), or birth weight and SEQ (r = -0.078 and p = .593).

In a logistic regression model, GA and BW did not significantly affect the SEQ (in group 1: $\beta = 0.2$, p = .27 and $\beta = -0.50$, p = .06, respectively; in group 2: $\beta = -0.07$, p = .78 and $\beta = -0.01$, p = .94, respectively). Also, by

adjusting GA and BW, SEQ was not significantly different between two groups (p = .61).

Four eyes (10.5%) in group1 and 4 eyes (8.2%) in group 2 were myopic. None of our patients showed high myopia (SEQ more than -5.00 D) or strabismus at the time of follow ups.

For better comparison, the spherical equivalent of refractive errors were divided into three groups (SEQ> +3.00 D, +3.00 \ge SEQ \ge 0, 0> SEQ \ge -3.00) and the number of subjects in each group was illustrated in Figure 1. Also, 9 infants (23.7%) in group1, and 5 infants (10.2%) in groups 2, had refractive anisometropia which was not significantly different between groups (χ^2 (1, n = 87) = 2.87, *p* = .081). Mean anisometropia was 0.47 ± 0.50 D (plus range: 0.0 to 1.75) in group 1, and 0.39 ± 0.54 D (plus range: 0.0 to 2.38) in group 2.

Discussion

Intravitreous bevacizumab injection has been described as a treatment by successful anatomical outcomes, which even provides better anterior segment development than laser therapy.^{5,10,14} Reports, state that patients who are treated with laser photocoagulation may have ROP regression with a single treatment while they have higher refractive errors in comparison with patients who are treated with IVB,¹⁵ and IVB injection may lead to less myopia and

Table 2. Refractive outcomes at 1 -year adjusted age in right and left eyes.

t-value	p-value
-0.240	.81
-0.449	.654

^eD, Diopter

	Group1	Group2	t-value	p-value
Spherical Equivalent (D) ^a Astigmatism value (D) (Minus cylinder)	$+1.26 \pm 0.86$ 0.63 ± 0.67	+1.37 ± 1.14 0.42 ± 0.62	-0.461 -1.53	.646 .131

^aD, Diopter

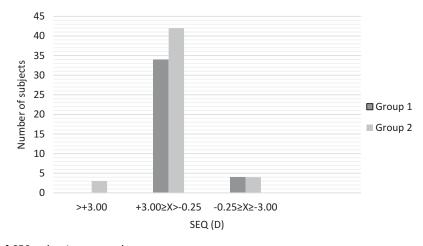


Figure 1. Distribution of SEQ value in two study groups.

astigmatism.¹⁴ Kuo et al. in their study showed that there is no significant difference in the myopic status of patients who treated with these therapeutic regimens.¹⁶ Also, Issac et al. found no difference in visual acuity and refraction in two groups. They concluded that both IVB and laser therapy result in good structural outcome.¹⁷ Mueller¹⁸ reported similar findings. They stated that after 12 months, the spherical equivalent was comparable between infants treated with IVB or laser photocoagulation. The presence of controversy between the results reveals that more studies with longer follow-ups on different treatment option are needed. According to previous studies, refractive error in babies who are born premature, tend to be more similar to full-term babies at older ages. However, this group still has a higher incidence of myopia and astigmatism than their full-term peers.¹⁹ Holmstrom et al.,²⁰ in 10 years follow-up of premature infants found that spherical equivalent refractive development happens in similar courses at 6 months, 2.5 years and 10 years and is not related to the stage of ROP. They stated that refraction at 2.5 years can be a better predictor of refractive status in older ages. According to Holmstrom study, refraction at 6 months is not reliable to anticipate the amount of remaining refractive error at the age of 10 years. On the other hand, early detection of refractive errors is important and the results of studies with shorter follow-up times may be helpful in planning screening protocols for infants with ROP. Although, refraction has been proposed to be more reliable in older ages, according to our findings, it is comparable between two groups at 1-year-old adjusted age. However, reliable results are mandatory when we want to consider a prescription. Compared with previous studies, our work was performed on a larger sample size, and in order to obtain more precise findings, we used both Retcam and indirect ophthalmoscope for ROP diagnosis.

Gunay et al.²¹ in their study compared refractive and biometric results of IVB injection, laser therapy and

spontaneous regression of ROP at 1 year adjusted age and found no significant difference of SEQ between groups. Similar to their results, we found that at 1-yearold corrected age, there was no significant difference of SEQ between groups. However, more subjects, (45 eyes) in group 2 had plus Rx as compared to group 1 as shown in Figure 1.

Based on previous reports, premature infants with ROP had steeper keratometry readings and shorter axial lengths, which can lead to a more myopic refractive error in older ages.^{22,23} Gunay, believes that IVB is a safe treatment for premature infants with ROP, without interrupting anterior segment development of their eyes.

Snir et al.²² compared full-term and preterm infants with mild ROP. They found that at the age of 40 weeks, ROP patients were more myopic than full terms. Snir, states that at the age of 10 months, mild ROP patients have mild hyperopia and full-term infants have moderate hyperopia (+1.36 D versus +2.46 D). This is in agreement with the view of Cook²⁴ who stated that premature infants have steeper corneas and shorter axial lengths than full-term babies. He believes that these differences are correlated to the severity of ROP and are more prominent in patients who were undergone laser therapy. According to previous studies, the incidence rate of anisometropia is higher in patients with ROP and increases with the severity of ROP.²⁵ Wang et al., in a longitudinal 7-years study on the refractive development of the children with regressed ROP, found that in severe ROP children, anisometropia and astigmatism increases with age while in mild or no ROP group, little changes in refraction happens. Also, previous reports have shown that after 1 year, anisometropia status was similar between preterm infants with no ROP, regressed ROP and full-term infants.⁴ In our study, more anisometropic eyes were found in IVB treated group. Although the difference with the

spontaneously regressed ROP group was not significant, anisometropia should be considered as an amblyogenic factor when planning for the screening of the ROP children. It has been well documented that the prevalence of strabismus increases in low birth weight population. On the other hand, the age of development of strabismus is not clear.⁸ Although, at the time of our study none of our cases had strabismus, it should be considered as a possibility in future followup care of these infants.

Issac et al.¹⁷ found a more myopic refractive error at <1 years of age as compared to the current study. There are many studies that have monitored refraction in ROP treated with IVB, some of them found more myopic findings as compared to our results.^{26,27} These findings may be related to the differences in stages and/or zones of subjects included in the studies. Lower birth weight of the patients can also be a contributing factor to the more myopic refractive error which has been reported in other studies.^{17,26} In our study, GA and BW were significantly different between two groups. Although, infants with lower GA and BW were more myopic and less hyperopic, the effect of these factors on final SEQ was not significant. Friling in a study on preterm and full-term infants found that higher keratometric readings were noted in babies with lower BW and GA.²⁸ But Snir found that GA and BW had no impact on keratometric and refractive findings of preterm infants with no or mild ROP.²² On the other hand, it has been reported that infants with low BW are more likely to have higher myopic refractive errors in adulthood.²⁹

Our study was associated with some limitations. A larger sample size and longer follow-up period can better confirm the results. Contralateral eye studies on infants with unilateral IVB injection, and considering another group of study, consisting full-term babies may provide a better comparison of refractive outcomes in premature and mature babies. Also, a group of laser-treated children should be included in this study in order to ascertain the treatment effect on refractive outcomes. Performing biometric tests is also helpful to find correlations between anatomic and refractive changes in subjects and to reveal the actual influence of treatment on refractive outcomes.

Although our results showed no significant difference in SEQ between two groups, it does not reflect the quality of vision of these babies. Since, group 2 had a better retinal status they may have a better visual prognosis. So, more studies are warranted on the visual function of these neonates at older ages.

In summary, at 1 -year adjusted age, refractive findings of premature newborns with ROP who were treated with IVB, were not significantly different with the infants with spontaneous regression of ROP. Further studies with longer duration are warranted to elucidate the effects of IVB on emmetropization process. Biometry assessments would be helpful in this regard.

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Disclosure of interest

The authors report no conflict of interest.

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