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Factors Affecting Refractive Status in Babies Followed for Retinopathy of Prematurity; 2 Years Outcomes: A Retrospective Research

Prematürite Retinopatisi Nedeniyle Takip Edilen Bebeklerde Refraktif Durumu Etkileyen Faktörler; 2 Yıllık Sonuçlar: Retrospektif Bir Çalışma

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ABSTRACT Objective: To evaluate the refractive changes in the first two years of life and to investigate the effect of prematurity, retinopathy of prematurity (ROP) and its treatment on refraction. **Material and Methods:** This is a single center retrospective study. Ninety eight patients and 196 eyes were investigated between 2016 and 2019. Refractive status was evaluated at 6th month, 1st and 2nd years. **Results:** Mean spherical value was +2.10±2.36, +1.50±2.13 and +1.13±2.30 at 6 months, 1 year and 2 years, respectively. There was a positive correlation between gestational week (GW) and spherical equivalent (SE) values at each follow-up (r=0.21 p=0.002, r=0.26 p=0.000, r=0.28 p=0.000 respectively). SE values in cases born before and after 32 GW did not show any difference at 6th month (p=0.138) at the 1st year and 2nd years, SE values were lower (p=0.028, p=0.009). All cases of high myopic were aggressive posterior-ROP (APROP). Treated and untreated groups were compared and significant differences were observed (p=0.000, p=0.000, p=0.000, respectively). The study did not reveal any significant differences between diode laser and intravitreal bevacizumab group (p=0.22, p=0.634 and p=0.885, respectively). Astigmatism is not affected by these factors. **Conclusion:** Higher myopia was detected in those born under 32 GW at 1st year and 2nd years, in APROP cases and in those treated for ROP. Severity of ROP disease itself significantly affects refraction in these type of cases. Astigmatism is not affected by these factors.

Keywords: Retinopathy of prematurity; refractive errors; neonatal screening; lasers; intravitreal injections

ÖZET Amaç: Yaşamın ilk 2 yılındaki refraktif değişiklikleri değerlendirmek ve prematürite, prematüre retinopatisi [retinopathy of prematurity (ROP)] ve tedavisinin refraksiyon üzerindeki etkisini araştırmak. **Gereç ve Yöntemler:** Bu tek merkezli retrospektif bir çalışmadır. 2016 ve 2019 yılları arasında 98 hasta ve 196 göz incelendi. Refraksiyon; 6. ay, 1 ve 2. yılda değerlendirildi. **Bulgular:** Ortalama sikloplejinli sferik eşdeğer (SE) 6. ayda +2,10±2,36, 1. yılda +1,50±2,13 ve 2. yılda +1,13± 2,30 idi. Altıncı ay, 1 ve 2. yıl gestasyon haftası [gestational week (GW)] ile SE değerleri arasında pozitif korelasyon vardı (sırasıyla r=0,21 p=0,002, r=0,26 p=0,000, r=0,28 p=0,000). 32 GW öncesi ve sonrası doğanlarda SE değerleri 6. ayda farklılık göstermedi (p= 0,138). Ancak 1 ve 2. yılda SE değerleri farklıydı (p=0,028, p=0,009). Yüksek miyop vakalarının tümü agresif posterior ROP (APROP) idi. Tedavi edilen ve tedavi edilmeyen gruplar karşılaştırıldığında SE değerlerinde anlamlı fark izlendi (sırasıyla p=0,000, p=0,000, p=0,000). Diod lazer ve intravitreal bevacizumab grubu arasında SE değerlerinde anlamlı fark yoktu (sırasıyla p=0,22, p=0,634 ve p=0,885). Astigmatik değerlerin ve eksenin dağılımında hiçbir grupta anlamlı fark yoktu. **Sonuç:** Birinci ve ikinci yılda, 32 gebelik haftasından önce doğanlarda, APROP tanısı alanlarda ve ROP tedavisi görenlerde miyopi anlamlı derecede fazladır. ROP hastalığının ciddiyeti bu tür vakalarda refraksiyonu önemli ölçüde etkiler. Astigmatizma bu değişkenler ile ilişkisizdir.

Anahtar Kelimeler: Prematüre retinopatisi; refraksiyon kusurları; yenidoğan taraması; lazerler; intravitreal enjeksiyon

The eye structure of newborns should be viewed from a different perspective than a mature eye. Prematurity, appears to interfere with the physiological development of the eye.[1,2] The premature eye also faces a risk: retinopathy of prematurity (ROP). The disease and its treatment may cause temporary or permanent changes in the eye that affect the vision.[3,4] Several researchers have evaluated refraction in pre-

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maturely born infants.[5,6] Some authors claim that prematurity does not affect refraction, whereas ROP disease does.[7] The others argue that early stages of ROP do not have an effect on refraction, however refraction is affected during later stages.[8] Although some scholars claim that refractive changes are more myopic, visual outcomes are worse in patients who have received treatment than in those who were born mature, who did not develop ROP, or who improved without treatment.[9] It is commonly viewed that, while prematurity affects refractive results with biometric parameter changes, ROP influences and aggrevates biometric changes because of ischemia of the anterior segment and retina; in addition to this laser-treatment promotes scar formation in the lesion. There is also an ongoing debate about the effect of anti-vascular endothelial growth factor (VEGF) on refraction.

In this study, ocular changes of newborns and preterm babies were evaluated from refractive perspective; however, anatomical parameters such as axial length and anterior chamber depth were not investigated. We examined refractive distribution in full-term infants, and compared those born before and after 32 gestational week (GW) in terms of spherical equivalent (SE) and cylindiric values. In addition to this, we investigated the effects of prematurity, ROP disease and its treatment on refraction.

MATERIAL AND METHODS

This study was planned to investigate how refraction values are distributed among patients who have undergone ROP screening. This is a single center retrospective study.

Patients who underwent fundus examination at the Istanbul Training and Research Hospital between January 2016 and June 2019 were included in the study. This study was conducted with the approval of the İstanbul Training and Research Hospital Clinical Research Ethics Committee, dated 09.08.2019, numbered 1932. The research adhered to the Helsinki Declaration.

Medical records on gender, GW, birth weight (BW), duration of the stay in the intensive care unit (ICU), diseases and treatments were collected. Ocular findings were recorded.

Three separate groups were composed of those who were born before 32 weeks or after 33 weeks, those with and without ROP, those who received ROP treatment, and those who did not. SE values were investigated in each group.

The patients with any stage of ROP were evaluated as ROP group. Initially, 160 subjects were selected; however, 62 subjects were later excluded due to incomplete medical information. As a result, the analysis of 98 cases and 196 eyes were included for the final analysis.

Examination and Screening for ROP: ROP examination was performed by indirect ophthalmoscopy (Omega 500, HEINE Optotechnik, Herrsching Ammersee, Germany) using eye speculum, scleral depressor, and 20 or 28 diopter lenses. ROP was diagnosed according to the International Classification Criteria for Retinopathy of Prematurity.[10] The zone and stage of ROP recorded at each visit and the most advanced stage was accepted as the stage of ROP.

The parents were informed about the treatment options, efficacy and possible complications. Written informed consent was obtained at each procedure.

Diode laser photocoagulation (Iridex OcuLight SL/SLx 810 nm diode laser, Mountain View, CA, USA) was performed within 72 hours in threshold and high-risk pre-threshold (type 1) disease described in the report of early treatment for-ROP.[11]

Aggressive posterior-ROP (APROP) was defined as increased dilation and tortuosity of the posterior pole vessels in all quadrants with flat neovascularization in Zone I or posterior Zone II. Cases with APROP were performed intravitreal anti-VEGF (0.625 mg/0.025 mL bevacizumab). The pupil was dilated with 2.5% phenylephrine and 0.5% tropicamide before intravitreal injection. Topical anesthesia was performed using 0.5% proparacaine hydrochloride. Intravitreal bevacizumab was injected 1.5 mm posterior to the limbus in the temporal inferior quadrant via a 30 G needle. Two weeks after the injection, the non-regression of plus disease was evaluated in one eye as non-responsive, and additional laser treatment was applied. This eye was excluded from the comparative analysis. In treated

group, retinal vascularization was completed in the following examinations without additional treatment except the one eye mentioned earlier. Subjects without ROP and with incomplete vascularization of retina were checked until retinal vascularization was completed.

Refractive Examination: All patients were performed refractive examination routinely at 6 months, 1 and 2 years. During each visit, cycloplegic refraction was performed, using streak light retinoscope (Keeler Professional Streak Retinoscope, UK). Cycloplegic retinoscopy examination was used for refractive evaluation. Each eye was evaluated separately. 1% cyclopentolate was used for cycloplegia. One drop was administered three times with the 10-minute interval. Refractive errors were calculated as follows: diopter (D) was expressed as "spherical equivalent refraction (SER): SER=spherical refraction+1/2 cylindrical refraction". The distribution of diopter was expressed as mean diopter X±standard deviation (SD).

Refractive errors were defined as follows: high myopia (SE>-5 D), low myopia (SE: -5 D to -1 D), emmetropia (SE: -1 D to +1 D), low hyperopia (SE: +1 D to +4 D) and high hyperopia (SE>+4 D). Astigmatism was categorized according to cylindrical values: low (<-1 D), moderate (-1 D to-2 D) and high astigmatism (>-2 D). Cylindrical axis was expressed as follows: with-the-rule (WTR: 75-105), against-the-rule (ATR: 0-15 and 165-180) and oblique astigmatism (OBL: 16-74 and 106-164).

STATISTICAL ANALYSIS

SPSS version 22.0 was used for statistical analysis. Results were evaluated at 95% confidence interval and $p<0.05$ significance level. The distribution of the variables was checked using Shapiro-Wilk test. The prevalence of myopia, hyperopia and astigmatism were compared with the results of Chi-square test. Fisher exact test was used when 20% of theoretical frequency was <5; Student's' t-test was used for small independent quantitative data; and ANOVA test was used for variance analysis. A value of $p<0.05$ was considered statistically significant. When the ANOVA results were different, multiple comparison tests (Tamhane's T2 multiple comparison test) were applied to determine which groups had different results. Pearson correlation coefficient was determined by correlation among the length of ICU therapy, birth weight, gestational age and SE.

RESULTS

A) SE Values in All Cases: The study consisted of 196 eyes of 98 premature infants. 60 (61%) infants were male and 38 (39%) were female ($p>0.05$). Mean gestational age was 32.05±4.26 (24-37) weeks. Mean BW was 1,885±971 (560-410) g. Mean ICU stay was 28.78 days.

There was a mild positive correlation between the length of stay in the ICU and SE values at 6 months, 1 and 2 years ($r=-0.20$ $p=0.005$, $r=-0.22$ $p=0.001$, $r=0.25$ $p=0.000$ respectively). Of the cases, 45.9% were born prior to 32 GW (45 infants n=90 eyes) whereas, 54.1% cases born after 33 weeks (53 infants n=106 eyes).

Mean spherical value was +2.10±2.36, +1.50±2.13 and +1.13±2.30 at 6 months, 1 year and 2 years respectively.

The percentile of the SE value was widely distributed at the 6th month compared to SE at 1st year and 2nd years (Figure 1).

When SE values are classified as high/low hyperopia, emmetropia, and high/low myopia, the number of cases and percentage in each group are shown in Table 1. A graphic representation of this table is also shown (Table 1).

The first SE values at 6 months were correlated with the values of 1 year and 2 years. ($r=0.93$ $p=0.000$, $r=0.91$ $p=0.000$, respectively).

B) Astigmatic Values in All Cases: Mean cylindric values was -1.42±0.89, -1.19±0.91 and -0.95±0.82 at 6th monht, 1st year and 2nd year respectively.

When cylindric values are grouped as low (<-1 D), modarate(-1 D to-2 D) and high astigmatism (>-2 D), distribution of percentile is shown in Table 2a and the cylindrical axis are grouped as the rule, against the rule and oblique astigmatism, determined percentiles are shown in the Table 2b (Table 2).

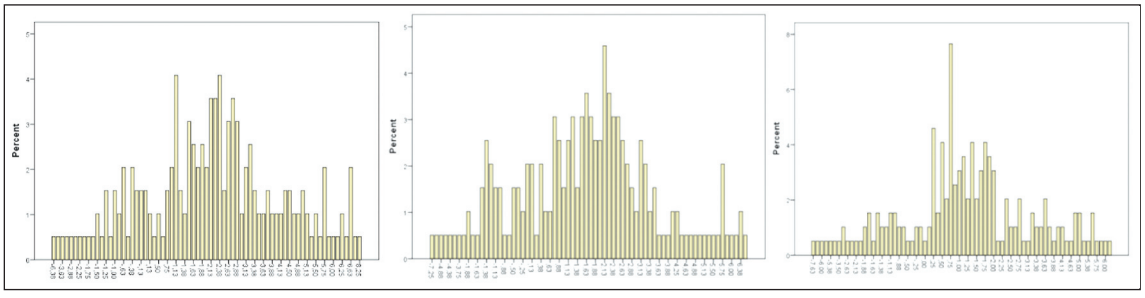
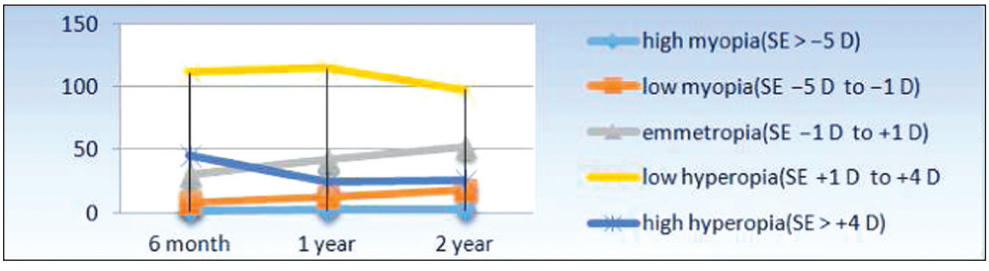


FIGURE 1: Distribution of spherical equivalent (SE) values at 6th month, 1st year and 2nd year. **a)** Sixth month SE distribution, **b)** First year SE distribution, **c)** Second year SE distribution.

TABLE 1: Distribution and frequency table (a) and (b) of SE number of cases.

a)	High myopia (>-5 D)	Low myopia (-5D to -1 D)	Emmetropia (-1D to +1 D)	Low hyperopia (+1D to +4 D)	High hyperopia (>+4 D)
6th month SE	1% (n=2)	9.2% (n=18)	16.8% (n=33)	54.1% (n=106)	18.9% (n=37)
First year SE	1% (n=2)	14.3% (n=28)	20.9% (n=41)	52% (n=102)	11.7% (n=23)
Second year SE	2.6% (n=5)	13.8% (n=27)	32.1% (n=63)	41.8% (n=82)	9.7% (n=19)

b) **Changes in the number of cases with grouped refraction status in over time.**



SE: Spherical equivalent; n: Number of cases; D: Diopter.

TABLE 2: Distribution and frequency table of astigmatism (a) and cylindric axis (b).

a)	Low astigmatism (< -1 D)	Modarate astigmatism (-1 D to -2 D)	High astigmatism (> -2 D)
6th month cylindric	44.9% (n=88)	34.2% (n=67)	20.9% (n=41)
First year cylindric	59.7% (n=117)	26.0% (n=51)	14.3% (n=28)
Second year cylindric	69.4% (n=136)	20.9% (n=41)	9.7% (n=19)
b)	**OBL (16-74 and 106-164)**	**ATR (0-15 and 165-180)**	**WTR (75-105)**
6th month cylindric axis	35.7% (n=70)	62.8% (n=123)	1.5% (n=3)
First year cylindric axis	38.3% (n=75)	58.2% (n=114)	3.6% (n=7)
Second year cylindric axis	36.2% (n=71)	61.7% (n=121)	2% (n=4)

D: Diopter; n: number of cases; ATR: Against-the-rule; OBL: Oblique; WTR: With-the-rule.

C) Gestational Week and Refraction: Distribution of SE values according to GW can be seen in Table 3. SE values in babies born before and after 32 weeks did not show significant difference at 6 months (p=0.138). In the 1st year and 2nd year, SE values were statistically lower (myopic) (p=0.028, p=0.009) at Student t-test and were more myopic in group born before 32 GW. SE values at 1st and 2nd year were sig-

TABLE 3: Mean, standard deviation, maximum and minimum values of SE in each control in group before and after 32 GW.

Mean SE for each control	32 GW and before: 45 infants (n=90)	After 33 GW: 53 infants (n=106)	p values (Student t-test)
SE mean 6th month	+1.83 ±2.51 (minimum: -6.38, maximum: +6.63).	+2.34 ±2.21 (minimum: 2.25, maximum: +8.25)	p=0.138
SE mean 1st year	+1.11±2.52 (minimum: -7.25, maximum: +5.88).	+1.83±2.02 (minimum: -2.13, maximum: +6.88)	p=0.028
SE mean 2nd year	+0.67±2.51 (minimum: -7.63, maximum: +5.50)	+1.51±2.02 (minimum: -2.63, maximum: + 6.88)	p=0.09

SE: Spherical equivalent; GW: Gestational week.

nificantly lower (p=0.028; p=0.009). Pearson correlation analysis showed a positive correlation between GW and SE values in the 6th month, first and second years (r=0.21 p=0.002, r=0.263 p=0.000, r=0.289 p=0.000 respectively). Pearson correlation analysis also showed a positive correlation between GW, BW and SE values at each follow-up point as a natural relationship of GW and BW(r=0.14 p=0.046; r=0.21 p=0.002; r=0.23 p=0.001 respectively).

D) ROP and Refraction: When the distribution of SE values were evaluated according to ROP presence and stages, the distribution in Table 4 was observed. In this table, SE values of APROP cases are remarkable. All of the high myopic cases are APROP. Values shifted from low myopia to high myopia and high hyperopia to low hyperopia between the first year and second years, resulting in significant myopic shift.

E) ROP Treatment and Refraction: The treatment was applied to both eyes of all the patients who received ROP treatment. None of the patients had asymmetry at a level that could improve without treatment in one eye.

When treated and non-treated groups were compared by the ANOVA test, statistically significant differences were observed between the 6th months 1st and 2nd year (p=0.000, p=0.000, p=0.000 respectively).

Untreated group was compared to the anti-VEGF or laser-treated groups using Tamhane's T2 multiple comparison test, at 6th months 1st and 2nd years, and a significant difference was found between the untreated eyes and laser/anti-VEGF treated eyes at each control (p=0.000, p=0.001, p=0.000 respectively). Mean SE values of untreated eyes were +2.34 (±2.21), +1.83 (±2.02) and +1.51 (±2.02) at 6 months, 1 year and 2 years respectively. Treated eyes were more myopic. Mean SE values of laser-treated babies were -0.90 (±1.63), -1.32 (±1.83) and -1.55 (±1.48). These values were +0.58 (±3.93), -0.72 (±4.13), -1.28 (±4.45) at the cases who applied anti-VEGF.

The distribution of SE values according to laser-treated (n=10) and anti-VEGF treated eyes (n=14) is shown in Table 5. When two different treatment groups were compared, no significant difference was detected (p=0.221, p=0.634 and p=0.885, respectively).

The distribution of astigmatism values and axis in groups who were born before and after 32 GW, the distribution in cases with and without RP, and the distribution in treated and untreated groups were statistically evaluated; no significant differences in value were found in any group.

In 17 (17.3%) of 98 cases, correction was performed with glasses during the first 2 years. One of the laser-treated cases (20%) received glasses because of exodeviation. Three anti-VEGF-treated cases (42.8%) received glasses. Contact lenses were recommended to an anisometropic case with high myopia in only one eye.

Strabismus was observed in 12 cases, 1 in laser-treated cases, and 3 in anti-VEGF-treated cases.

DISCUSSION

Refraction in infants is one of the challenges of ophthalmology.

TABLE 4: Distribution table of spherical values by ROP stage.

	High myopia (SE > -5 D)			Low myopia (SE -5 D to -1 D)			Emmetropia (SE -1 D to +1 D)			Low hyperopia (SE +1 D to +4 D)			High hyperopia (SE > +4 D)		
STAGE of ROP	6th month	1st year	2nd year	6th month	1st year	2nd year	6th month	1st year	2nd year	6th month	1st year	2nd year	6th month	1st year	2nd year
Non-ROP (n=83)	0	0	0	2	5	5	12	22	28	57	48	42	12	8	8
Stage 1 (n=43)	0	0	0	7	9	11	9	7	8	14	17	17	13	10	7
Stage 2 (n=37)	0	0	0	1	0	1	2	7	16	25	26	17	9	4	3
Stage 3 (n=20)	0	0	0	3	7	6	9	4	10	7	9	4	1	0	0
APROP (n=13)	2	2	5	5	7	4	1	1	1	3	2	2	2	1	1
Total (n)	2	2	5	18	28	27	33	41	63	106	102	82	37	23	19

ROP: Retinopathy of prematurity; D: Diopter; SE: Spherical equivalent; n: Number of cases; APROP: Aggressive-ROP.

TABLE 5: SE and standard deviation in the treated eye.

Mean SE for each control	Laser-treated (n=10)	Anti-VEGF-treated eyes (n=14)	p value (Tamhane's)
SE mean 6th month	-0.90 ±1.63 (minimum: -3.63, maximum: +1.00)	+0.58 ±3.93 (minimum: -6.38, maximum: +6.63)	p=0.221
SE mean 1st year	-1.27±1.59 (minimum: -4.00, maximum: +0.88)	-0.72±4.13 (minimum: -7.25, maximum: +5.13)	p=0.634
SE mean 2nd year	-1.55±1.48 (minimum:-3.63, maximum: +0.63)	-1.28 ±4.45 (minimum: -7.63, maximum: +4.88)	p=0.885

SE: Spherical equivalent; n: Number of cases; VEGF: Vascular endothelial growth factor.

Full term newborn babies tend to have hypermetropic refractive status. The emmetropization process is fast during the first 2 years of life. In our study, the mean SE was +2.10±2.36 diopters at 6 months, +1.50±2.13 diopters at 1 year, and +1.13±2.30 diopters at 2 years.

In this study, the SE value was widely distributed initially, it tended to be around the center during later examinations. The accumulation around the center became more evident especially in the second year.

When SE values were grouped as high/low hyperopia, emmetropia and high/low myopia, the number of high hyperopic cases decreased rapidly in two years, the number of low myopic cases increased. In addition to this, a constantly steeper curve was observed in emmetropia (Figure 1a-c).

In early gestational ages, astigmatism is common and frequently greater than 1 D. Some researchers suggest the fact that astigmatism may change according to eye movements in newborns and may be associated with pulling the rectus muscles to the baby sclera.[12] In this study, the mean astigmatic value was -1.42±0.89 D at 6th months, -1.19±0.91 D at 1st year and -0.95±0.82 D at 2nd years. Over time, there was a decrease in astigmatic values. In this study, the total rate of low and moderate astigmatism was 79.1% at 6th months. While high and moderate astigmatism decreased, the frequency of low astigmatism increased (Table 2). The axis of the astigmatism is markedly ATR dominant, which continued until the age of two and the WTR rate was found to be quite low even at the age of two. Dobson et al. found that astigmatism was 83% and more ATR in the premature infants. In addition, Early Treatment Diabetic Retinopathy Study group found that axis of astigmatism was most frequently ATR.[13,14]

There are many studies in literature stating that prematurity affects refractive outcomes.[15,16] The progression of myopia in premature can be explained by the abnormal development of the refractive system.

In this study, the percentage of high myopia was 1% in 2 controls and 2% at the last one (Table 1). The rate of myopia was 9.2% and 14.3%, respectively in 2 follow-up and 13.8% at the last one. Larsson and Holmstrom found that the risk of refractive error was significantly higher in preterm babies compared to full-term babies after 10 years of follow-up. In Goktas' study, the prevalence of high myopia (above -5.0 D) and myopia (below -5.0 D) was found 12.5% and 22.5%, respectively, in 28 GW and preterm cases. Myopia was found 3.6% and 18.9% at 29 to 32 week groups and only 7.9% at 33 to 36 weeks groups.[17,18]

Studies that investigated the anatomical mechanism of refractive error, especially myopia, found that prematures with refractive error had shorter axial length, greater corneal curvature, shallower anterior chamber depth, and thicker lens compared to normal full-terms. More studies are needed to fully understand the mechanism.[16,19]

In our study, SE values in cases born before and after 32 GW did not show statistically significant difference at 6th months (p=0.138); conversely, at 1st and 2nd years SE values were statistically significant (p=0.028, p=0.009) and more myopic in a group born before 32 G. In Mao's study, infants were grouped according to gestational age (before/after 30 GW) and BW (under/above 1,500 g) to evaluate the correlation between refractive status and the beforementioned two variables.[20] At the same postmenstrual age, there was no significant difference between the groups (p>0.05).

Our study showed GW increases, the SE value increases, which means that it is more hypermetropic. On the contrary, low GW means more myopic SE values. Correlation analysis also showed a positive correlation among GW, BW and SE values in each follow-up point as a natural relationship between GW and BW. Contrary to Mao et al.'s study that argued that GW was effective only on early refraction values, we saw that the significant effect occured after the 6th month and this effect continued until the age of two.[20]

ROP may be an important factor leading to myopia progression. A few studies found that severe ROP or ROP requiring treatment could cause high myopia, while mild ROP or spontaneously regressed ROP did not cause high myopia.[21] APROP is characterized by interruption of retinal vascularization in the early stages and severe ischemia. Severe ischemia of the immature eye causes significant structural changes when it covers large retinal areas. In our study, the frequency of myopia was more than 1 and 2 in Stage 3 and APROP cases; the strength of the groups was not sufficient for statistical assessment. When cases were grouped before and after 32 GW, all high myopic cases were APROP that included cases born prior to 32 weeks. This is particularly striking. Ruan et al. found that APROP cases tended to have more serious refractive errors, especially high myopia and spherical anisometropia.[22]

This study investigated the effect of ROP on cylindrical values as well as on spherical values. The distribution of astigmatic values and axis in a group who were born before and after 32 GW, the distribution in cases with and without ROP, and the distribution in treated and untreated groups were statistically evaluated and no significant value was found in any group. Some scholars have investigated the effect of ROP on cylindrical values.[14,15,23,24] Hennein emphasized the importance of astigmatism in premature cases and stated that it was the most prevalent risk factor for amblyopia.[23] In their study, astigmatism was 18% in ROP group and 7% in non-ROP group but this difference was not statistically significant.[23] Ozdemir et al. found that astigmatism did not correlate with GW and BW. Kaya et al. found that premature infants with severe ROP were more likely to develop not only myopia but also astigmatism.[8,15] This study found the highest risk of astigmatism in eyes that had undergone peripheral retinal ablation.[14] Ouyang et al.'s study showed that cases with ROP and premature with non-ROP were not different and statically significant in terms of astigmatism.[24]

ROP treatments may affect refractive outcomes. Higher refractive error and higher correction may be necessary in treated eyes.[25] Our study showed that both treatments affect myopic refraction (Table 5). There is different SE between treated cases and just following cases. The untreated group, the anti-VEGF or laser-treated groups were compared at 6th months, 1st year and 2nd years and a significant difference was found between the untreated eyes and laser-treated

eyes at each control (p=0.000, p=0.001, p=0.000, respectively). Both laser and anti-VEGF-treated groups have higher myopic refraction. When two different treatment groups were compared, no significant difference was detected (p=0.221, p=0.634 and p=0.885, respectively).

Although it is controversial how anti-VEGF affects refractive outcomes, there are publications claiming that refractive results of anti-VEGF are more acceptable.[26]

Two different treatment types of ROP are not an equivalent alternative. The severity and type of the disease affect the choice of treatment. Several factors overlapping affect refractive results. Even the type and dose of intravitreal drug and the amount of laser therapy can be effective on refraction. There are publications claiming that bevacizumab causes more myopia than ranibizumab and there are studies investigating the effect of the number of laser spots on refractive results.[27,28] Laser treatment affects the tendency toward myopic via sclerochoroidal thinning and increase of axial length.[22,28] Another study examined refractive outcomes between laser and anti-VEGF treatment determined no significant refractive difference between laser and anti-VEGF treatment in the following 4 years in mean SE.[29]

Glasses were prescribed for 17.3% of babies and the rate of strabismus was 12.2% in the study cohort. This is higher than the society-based studies.[30] In laser-treated group, the glasses prescription rate was 20%, and in the anti-VEGF treated group the rate was 42.8%. Tolia et al. found that strabismus rate was 21.9% in Stage 2 or higher ROP group.[31]

There are some limitations to be mentioned in our study. First, this study is a retrospective, non-randomized control study. We evaluated those born over 32 GW as a control group. Third, the number of infants is relatively small, especially in treated group, which may reduce the strength of some statements. In addition, two years follow-up was irregular in the group that recovered without treatment. Moreover, 62 subjects were excluded from the study due to missing medical information at the beginning of the study. Ninety eight cases were analyzed and this amount of exclusion may have affected the results.

CONCLUSION

In the present study, the infants of up to 2 years of age were examined. We think that three follow-ups to the age of two are sufficient to detect refractive errors.

Even if ROP treatment is completed in premature cases, refraction examination has to be conducted regularly. Studies indicate that this process continues until young adulthood.

Patients born before 32 GW are at risk of developing refractive errors if they have ROP and were treated. Many studies have reported that diode laser photocoagulation causes myopic shift. Despite a few number of treated-cases in this study, it was still observed that treatment affected refraction but refractive results were not different among treatment alternatives. This situation may be related to the laser doses that we applied. We suggest that the severity of ROP disease itself significantly affects refraction as in APROP cases. Both early onset ischemia and differences in treatment modalities require keeping this group of patients separate from other ROP cases in terms of refractive errors. APROP cases should be carefully monitored.

There is no designated time to end screening for refractive errors. If no problem is detected, it is natural for premature babies to continue a routine eye-screening program. However, it should be kept in mind that refractive errors are more frequent, so examinations will be more frequent in premature groups. In addition, patients who have ROP follow-ups should be carefully monitored for strabismus.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tülin Öğreden;* ***Design:*** *Tülin Öğreden;* ***Control/Supervision:*** *Tülin Öğreden;* ***Data Collection and/or Processing:*** *Tülin Öğreden, Furkanüçtepe;* ***Analysis and/or Interpretation:*** *Tülin Öğreden, Furkanüçtepe, Hülya Güngel;* ***Literature Review:*** *Tülin Öğreden, Furkanüçtepe;* ***Writing the Article:*** *Tülin Öğreden, Furkanüçtepe, Hülya Güngel;* ***Critical Review:*** *Hülya Güngel;* ***References and Fundings:*** *Tülin Öğreden;* ***Materials:*** *Tülin Öğreden.*

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