RESEARCH ARTICLE / *Araştırma Makalesi*

Comparison of Intravitreal Ranibizumab and Diod Laser Photocoagulation Treatment for Retinopathy of Prematurity; Effects on Axial Lenght and Refractive Status

Prematüre Retinopatisinde uygulanan Diod Lazer Fotokoagülasyon ile İntravitreal Ranibizumab Tedavilerinin Gözün Aksiyel Uzunluğuna ve Refraktif Durumuna Olan Etkilerinin Karşılaştırılması

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Abstract

Objective	To evaluate the effects of diode laser photocoagulation and intravitreal ranibizumab (IVR) treatments on axial lenght and refractive status development in the treatment of retinopathy of premautrity (ROP). **(Sakarya Med J 2019, 9(1):141-147)**
Materials and Methods	The study included 82 eyes of 41 patients who were 1 year adjusted age, underwent primarily diode laser photocoagulation or 0.25 mg/0.025 ml IVR. Axial lenght (AL) and spherical equivalent (SE) parameters were compared.
Results	Patients divided into two groups. Group 1 had 34 eyes of 17 patients who underwent IVR treatment and group 2 had 48 eyes of 24 patients who underwent diode laser photocoagulation treatment. In group 1, AL were detected 19,86 ±1,104mm in right eyes and 19,73 ±1,062mm in left eyes. In group 2, AL were detected 19,90± 0,83mm in right eyes and 19,86 ± 0,842mm in left eyes (p>0.05). In group1 and 2, SE values were detected 0.44±2.053D and -0.02±3.07D in right eyes and 0.59±2.063D and -0.17±2.8 in left eyesD, respectively (p>0.05). There was no statistically significant differences between two groups about AL and SE values.
Conclusion	Myopia is seen higher in patients with ROP than healthy patients. Although using anti vascular growth factor in ROP has been increased last years, diode laser photocoagulation is the gold standart therapy. In our study we compared the effects of diode laser photocoagulation and IVR on AL and SE. We did not find any statistically significant difference. Further evaluation is needed.
Keywords	Retinopathy of Prematurity; Laser Photocoagulation; Ranibizumab; Axial Lenght; Refraction

Öz

Amaç	*Prematüre retinopatisi (PR) tedavisinde uygulanan diod laser fotokoagülasyon (LFK) ile intravitreal ranibizumab (IVR) tedavilerinin gözün aksiyel ve refraktif gelişimi üzerine olan etkilerini değerlendirmektir. (Sakarya Tıp Dergisi 2019, 9(1):141-147).*
Gereç ve Yöntemler	*Kliniğimizde PR nedeniyle primer ve tek tedavi olarak LFK ve ya 0.25 mg/0.025 ml IVR tedavisi uygulanmış ve düzeltilmiş olarak bir yaşını doldurmuş 41 infantın 82 gözü çalışmaya dahil edilmiştir. Hastaların biyometri ile aksiyel uzunlukları(AU) ölçülmüş, sikloplejik muayene sonucu elde edilen refraktif değerleri sferik eküvalan olarak karşılaştırılmıştır.*
Bulgular	*IVR grubunda 17 hastanın 34 gözü Grup-1, LFK grubunda ise 24 hastanın 48 gözü Grup-2 olarak ayrıldı. Grup-1'de AU; sağ gözde 19,86 ±1,104mm; sol gözde 19,73 ±1,062mm idi. Grup-2'de sağ göz için 19,90± 0,83mm sol göz için 19,86 ± 0,842mm idi.(p>0.05) Refraktif değerler Grup-1'de sağ göz için 0.44±2.053D ; sol göz içinse 0.59±2.063D idi. Grup-2'de ise sağ göz -0.02±3.07D, sol göz ise -0.17±2.8 idi.(p>0.05) Her iki grupta hem aksiyel uzunluk açısından hem de sferik eküvalan açısından istatistiksel olarak anlamlı fark tespit edilmemiştir.*
Sonuç	*Prematüre retinopatili bebeklerde myopi gelişme oranı sağlıklı bebeklere göre daha yüksektir. Prematüre retinopatisi tedavisinde son yıllarda anti vasküler büyüme faktörü (Anti-Vebf) kullanımı hızla artmakla beraber LFK tedavisi altın standart tedavi olarak kullanılmaktadır. Çalışmamızda İVR tedavisi ile LFK tedavisinin aksiyel uzunluk ve sferik eküvalan değerleri üzerine yaptıkları etkiyi araştırdık ve bir fark bulamadık ama bu konuda daha fazla bilimsel çalışmaların yapılması gerektiğini düşünüyoruz*
Anahtar Kelimeler	*Prematüre retinopatisi; Lazer Fotokoagülasyon; Ranibizumab; Aksiyel Uzunluk; Refraksiyon.*

INTRODUCTION

Retinopathy of prematurity(ROP) is a proliferative vascular disease which is the preventable common cause of the blindness in preterm infants.[1] In pathogenesis, mediators especially anti-vascular growth factor (anti-VEGF) released from the avascular retina is particularly responsible for the disease.[2] Gold standard treatment of the disease is argon laser photocoagulation.[3] In addition, in literature, there are a lot of studies which is about successful treatment of the ROP with anti-VEGF agents. Particularly, in ROP cases involving the posterior pole of the retina, because of the low activity and high ocular morbidity of the laser photocoagulation treatment, anti-VEGF agents are preferred in therapy. Although bevacizumab is the most popular anti-VEGF agent, ranibizumab is one of the anti-VEGF agents which isused in the treatment of the ROP.[4,5]

In studies, it has shown that prematurity is a factor affecting the axial development of the eye.[6] It has also been shown that infants who have undergone laser photocoagulation therapy due to the ROP, considerable changes in the refractive status of the eye has been detected.[7] In recent years, several studies have reported extremely positive outcomes after intravitreal bevacizumab (IVB) treatment for ROP, which resulted in less refractive error than laser photocoagulation.[8,9] However, the reasons for these changes have not yet been fully clarified.

The aim of the study is to compare the effects of diode laser photocoagulation treatment and intravitreal ranibizumab (IVR) treatment on axial length and refractive status development in the treatment of ROP.

MATERIAL and METHODS

This study was conducted in tertiary ROP Diagnosis and Treatment Center byexamining the patient records retrospectively between January 2016 and January 2017. The study population consisted of infants who were 1 year adjusted age. Approval was obtained from the local ethics committee for the study. The study conformed to the tenets of the Declaration of Helsinki. This study is observational descriptive study.

The study included a total of 41 infants, who were organized into the following two groups: Group 1, which comprised infants treated with IVR monotherapy for ROP; Group 2, which comprised infants treated with laser photocoagulation for ROP. The first ophthalmological examination was performed by experienced ophthalmologist with indirect ophthalmoscope at 4 weeks after birth (Gestational age (GA) ±27 weeks) or 31 weeks of corrected GA (GA± 27 weeks). The pupil was dilated with tropicamide 0.5% andphenylephrine 2,5%. Ophthalmologist used 20D and 28D lenses, sterile lid speculum, and scleral depressor. The diagnosis was based on the guidelines of the International Committee for the Classification of ROP.10 Treatment decisions were made according to the Early Treatment for ROP (ETROP) study criteria.3 All findings were recorded. Infants who developed type 1 ROP defined by the Early Treatment for ROP(ET-ROP) study were provided the an option of IVR or laser treatment after a thorough discussion with their parents.

Laser photocoagulation treatment was conducted in Premature Intensive Care Unit. For laser photocoagulation treatment, the infant was sedated with ketamine under the supervision of an attending neonatologist. Laser photocoagulation treatment was performed with an indirect laser at wavelength 810-nm head-mounted diode laser (Iridex; Oculight SL, Mountain View, California).

Intravitreal ranibizumab treatment was conducted in operating room. For IVR treatment, a lid speculum was first placed in the eye and then 0.5% proparacaine HCl and 0.5% and 5% povidone-iodine were placed into the eye. An injection of ranibizumab 0.25 mg/0.025 mL was introduced into the vitreous with a 32-gauge needle at 1 mm behind the limbus.

After laser photocoagulation treatment or IVR treatment

all infants underwent fundus examination regularly until recovery.

Infants who had congenital anomalies required additional therapy (such as IVR and laser photocoagulation) or received different anti-VEGF agent, underwent any ocular surgery was excluded. All patients were included in this study except exluded patients and uncontrolled patients.

Cycloplegic refractions were performed after applying three drops of 1%cyclopentolate (an interval of 10 minutes) using a handheld autorefractometer (Welch Allyn; Sure Sight Autorefractor, New York). Three measurements were obtained for each subject. If an inconsistency was observed in these consecutive measurements, refractive assessments continued until at least 3 coherent refractive values were obtained. Refractive results were recorded as spherical equivalent (SE) powers. Axial length parameter was assessed using an ultrasonic biometry device (Nidek; US-4000 Echoscan, Japan). A total of 5 measurements of axial length were obtained for each subject and average readings were utilized for statistical analysis.

Data analysis was conducted using SPSS V.16.0 (SPSS Inc., Chicago, IL). Patients were classified into 2 groups, Group 1 was intravitreal ranibizumab treatment group and Group 2 was laser photocoagulation treatment group. Qualitative data and demographic data were compared among groups using the Chi-Square test. T-test was used to analyze quantitative variables. A difference with $p<0.05$ was considered significant.

RESULTS

Group 1 had 34 eyes of 17 patients and group 2 had 48 eyes of 24 patients. The demographic data of the patients are given in Table 1 in detail. There was not any statistically significant difference between groups in terms of gestational age, birth weight, treatment week and follow-up period. (Table 1)

After treatment in both groups, both plus disease and ROP were completely regressed, no additional treatment was given to any of the patients. Depending on the treatment modalities, none of the serious complications such as cataract, endophthalmitis, anterior segment ischemia, retinal detachment, and glaucoma were observed. In adjusted first age, anterior segment examination and fundus examination were normal. There was not ectopic macula or abnormal optic disc in any patient. In ranibizumab group all patients had full vascularisation up to ora serrata at last follow up.

In Group 1, 3 patients had stage 3 disease and 12 patients had zone 1 disease. In Group 1, axial lenght were detected 19,86 ±1,104mm in right eyes and 19,73±1,062mm in left eyes. In Group 2, axial lenght were detected 19,90 ± 0,83mm in right eyes and 19,86±0,842mm in left eyes ($p>0.05$). In Group 1, spherical equivalent values were de-

Table-1: Demographic properties of the patients.

	IVR N=17	LFK N=24	P* value
Gestational age (week)	28,00±3,00 (24-35)	28,46±3,09 (23-34)	,639
Birth weight (Gram)	1190,59±485,71 (640-2200)	1174,17±363,11 (540-1770)	,902
Treatment week (week)	35,65±1,72 (32-39)	36,27±1,14 (34-39)	,170
Follow-up period (week)	14,41±4,13 (14-20)	16,02±2,94 (14-22)	,153

IVR:Intravitreal Ranibizumab; LPC:Laser Photocoagulation

tected 0.44 2.053D (between -2.0D and +4.0D) in right eyes and 0.59 2.063D (between -2.0D and +5.0D) in left eyes. In Group 2, spherical equivalent values were detected -0.02 3.07D (between -8.0D and +5.0D) in right eyes and -0.17 2.8D (between -8.0D and +5.0D) in left eyes. There was not statistically significant difference in axial lenght values in right and left eyes (p values: 0.906, 0.648; respectively). There was not statistically significant difference in spherical equivalent values between groups (p values: 0.593, 0.353; respectively). (Table 2 and 3)

Table 2. Comparison of Axial lenght and refractive error in right eyes

VARIBLES	GROUP 1 RIGHT EYES	GROUP 2 RIGHT EYES	P VALUE
AXIAL LENGHT (mm)	19.86±1.104	19.90±0.83	0.906
SPHERİCAL EQIVALENT (Diopter)	0.44±2.053	-0.02±3.07	0.648

Table 3. Comparison of Axial lenght and refractive error in left eyes

VARIBLES	GROUP 2 LEFT EYES	GROUP 2 LEFT EYES	P VALUE
AXIAL LENGHT (mm)	19.73±1.062	19.86±0.842	0.593
SPHERİCAL EQIVALENT (Diopter)	0.59±2.063	-0.17±2.8	0.353

DISCUSSION

Ocular disorders such as strabismus, anisometropia, amblyopia and refraction error in premature babies are more likely to develop than babies born in term. The most common reason for these disorders is the development of ROP.

Ablation treatment (laser photocoagulation and cryotherapy) has been used in ROP since the 1980s. Many authors reported that the prevalence of astigmatism, myopia and high myopia were higher in children who underwent ablation therapy than those without ROP.[11,12,13] The main causative reasons are not clear. We performed analysis of SE and axial lengths of patients with laser photocoagulation treatment and patients with IVR treatment in our study.

It has been stated in several studies that ablation therapy causes scarring and inflammation, resulting in an increase in refraction error.[14,15] Axer Siegel et al. was found that myopia(-5D‹) incidence was 31.3% and high myopia (›-5D) incidence was 23.9% after laser photocoagulation treatment.[11] Dhawan et al. reported that the myopia incidence was 80.4% and high myopia incidence was 31.5% in their study.[12]

Mean SE value was reported -3.17D by Paysse et al., -1.5D by Axer Siegel et al. and -0.4D by Lee et al. after photocoagulation laser treatment.[11,16,17] In our study, we found that the mean SE value is -0.02D in right eyes and -0.17D in left eyes after laser photocoagulation treatment. Our results were similar to the study of Lee et al.

In recent years, using anti-VEGF agents to treat ROP have become more popular. The effects of these agents on biometric parameters are still research topic. Salman et al.who used aflibercept in treatment of ROP, reported that myopia and high myopia incidences were 23.1% and 3.8%, respectively.[18] On the other hand, bevacizumab study conducted by Harder et al., they found that myopia and high myopia incidences were 17% and 9%, respectively.[19]

SE values were found 0.64D by Harder et al, -1.00D by Martinez-Castellanos et al.and -1.04D by BEAT-ROOP study.[8,19,20] Bevacizumab therapy was used in these three study. In our study, we used ranibizumab therapy, SE value was found 0.44D in right eyes and 0.59D in left eyes. Our results are similar to the study of Harder et al.

In literature, several studies reported the refractive outcomes following anti-VEGF therapy for ROP had lower refractive errors than laser ablation. For example, Harder et

al. detected that IVB group was less refractive error than laser photocoagulation treatment group.[19] Chen et al. reported that the IVB group was less myopic than the laser photocoagulation group in the patients who were followed for 2 years.[9] On the other hand, some authors indicated that there was no difference in the development of refraction errors between laser photocoagulation therapy and anti-VEGF therapy. For example, Gunay et al., they compared the IVB and laser photocoagulation treatment on SE values, they did not find statistically significant difference between the groups.[21] Hwang et al. who treated 28 patients with 6 month follow-up period, they did not find statistically significant difference in refraction values between the IVB and laser photocoagulation treatment groups.[22]

There are a few studies which compare the effects of ranibizumab and laser photocoagulation treatment on refraction status. Gunay et al. whose study had 3 groups; IVR, IVB and laser photocoagulation treatment, they reported that there was not any statistically significant difference in SE values between the groups.[23] Kabataş et al. found the similar results between IVR, IVB and laser photocoagulation treatment groups.[24] We treated 17 patients with ranibizumab and 24 patients with laser ablation and no difference was found between the 2 different treatments in SE values. this result might be due to the relatively lower number of subjects and relatively lower follow-up period. This issue needs to be further investigated with larger study population and longer follow-up period.

The mechanism of development of refractive error after treatment of ROP has not been fully understood. Corneal curvature, anterior chamber depth, lens thickness, vitreous thickness and axial length play a role in the development of refraction error. It is a known fact that babies are born as hyperopia. With the emmetropization, hyperopia recover. The one of the most important parameter in emmetropization is axial length. Axial length was found shorter in premature infants(ROP+ or ROP-) than term infants in the study of Cook et al.[25] In the same study, they reported that the axial length was affected by the ROP stages and the mean axial length decreased as the stage progressed. Similarly, Law et al. found that axial length was negatively correlated with the stage of ROP.[26]

Many authors have studied the effects of treatment on axial length. Yang et al. examined the 9 years old patients who underwent only laser photocoagulation treatment, they found that there was no significant difference in axial length between healthy individuals of the same age.[27] Iwase et al. studied the effects of the size of the photocoagulation area on axial length and they reported that there was no significant difference between the 360-degree laser photocoagulation therapy group and partial laser photocoagulation group.[28] Lin et al. compared the effects of ranibizumab and bevacizumab treatment on axial length, they did not find any difference between groups.[29] Chen et al. whose study had 3 groups; IVB, IVB+laser photocoagulation, and IVB+ lens-sparing vitrectomy. They reported that there was no significant difference in axial length between the groups.[9] In the same study, there was no association between myopia and axial length, they indicated that myopia may be associated with anterior segment parameters.

There are very few studies in the literature investigating the effect of IVR treatment and laser photocoagulation treatment on axial length. Gunay et al. found that the axial length had no statistically significant difference between the groups receiving IVB, IVR and laser photocoagulation treatment.[23] In our study, we detected that the axial length in the IVR treatment group was 19,86±1,104mm in right eyes and 19,73 ±1,062mm in left eyes. In the laser photocoagulation treatment group, we found the axial length 19,90 ± 0,83mm in right eyes and 19,86 ± 0,842mm in left eyes. There was no statistically significant difference between right and left eyes in terms of axial length in both groups. We think that axial length is not affected by either laser photocoagulation treatment or IVR treatment and we also think that refraction error is not directly related to the axial length.

ROP not only affects vascularisation but also foveal structure. There have been reports that patients with a history of ROP examined by spectral domain optical coherence tomography were more likely to show abnormal foveal development than normal subjects.[30] In Turkey, Erol et al. detected cystoid macular edema in 38% of ROP patients.[31] Some authors have suggested that cystoid macular edema in prematurity may be related with vascular endothelial growth factor.[32,33] Furthermore, the treatment modalities of ROP, laser photocoagulation and anti-vegf treatment, can affect the structure of fovea. These effects can cause low vision. So, ophthalmologists should investigate the macular structure in patients with ROP with optical coherence tomography.

Limitations of the study are; the lack of a control group consisting of non-premature infants, lack of laser spot number, the number of patients and the follow-up period were relatively small and short, and the anterior segment parameters were not considered.

In conclusion, the methods used in PR treatment are developing rapidly in recent years. The effects of the treatments on ocular parameters are being investigated. We compared the effects of laser photocoagulation treatment, the gold standard treatment, and lower molecular weight ranibizumab on SE and axial length. We found no statistically significant difference between the two parameter values between the two groups. We believe that studies involving larger patient populations and anterior segment parameters should be undertaken in this regard. We think that our study is important because there are few articles in the literature comparing laser photocoagulation treatment and IVR treatment.

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