The Effect of Outer Retinal Layer Thickness on Visual Acuity in Retinal Vein Occlusion After Resolution of Macular Edema

Berrak Şekeryapan Gediz[1], Yasemin Özdamar Erol[2], Sibel Doğuizi[1], Büşra Dilara Yıldırım Erdal[3], Müge Pınar Çakar Özdal[2]

ABSTRACT

Purpose: To evaluate the relationship between outer retinal layer thickness (ORLT) and visual acuity (VA) in patients with retinal vein occlusion (RVO) after resolution of macular edema (ME) with intravitreal injections.

Material and Methods: The study included patients who received loading dose of intravitreal ranibizumab (IVR) forME secondary to unilateral RVO and had no ME in optical coherence tomography (OCT) obtained on month 12. The contralateral eyes of the patients were employed as control. ORLT was measured using automated segmentation feature in OCT. The RVO and control groups were compared regarding ORLT and relationship between ORLT and VA was assessed within RVO group. A p value <0.05 was considered as statistically significant.

Results: The study included 156 eyes of 78 patients. Of the patients, 70.5% had branch RVO and 29.5% had central RVO. There was a significant increase in mean VA on month 12 in the RVO group compared to the baseline (p <0.01). In the RVO group, dexamethasone (DEX) implant was given to 59% of the patients in addition to IVR. In RVO group, ORL thickness in M, N1, S1 and S2 segments were significantly lower than the control group (p <0.05, all values). The ORL thickness in M, N1, T1, T2, S1 and S2 segments were significantly lower in eyes received at least one DEX implant compared to eyes received no DEX implant (p <0.05, all values). There was a significant correlation between the mean VA value in the RVO group on month 12 and ORL thickness in segment M (p <0.01).

Conclusion: In RVO patients, subfoveal ORLT measured after resolution of ME is thinner in occlusion eyes than in healthy eyes. The significant ORLT decrease in eyes with DEX than in eyes received DEX implant compared to those received no DEX implant can be explained by the fact that DEX was given to patients with a more severe course of ME. The decrease in subfoveal ORLT resulting in lower VA suggested that RVO can lead to photoreceptor and/or retinal pigment epithelium degeneration in the long term.

Keywords: Dexamethasone implant, macular edema, OCT, outer retinal layer thickness, ranibizumab, retinal vein occlusion.

INTRODUCTION

Macular edema is most common cause of vision loss in retinal vein occlusion (RVO)[1]. However, it should be noted that no visual gain is achieved despite regression of macular edema in some patients[3]. Although cause of vision loss at long-term hasn't been fully understand, it is thought that loss of vision develops due to irreversible photoreceptor injury and/or neuronal degeneration, supported by electrophysiological studies[4].

Today, together with advances in optical coherence tomography (OCT) technologies, it has become possible to obtain high-resolution retinal images. The ability to perform segmentation and mapping thickness of retinal layers allows assessment of diseases that affect specific retinal layers. and to map segmentation. In the literature, the majority of studies analyzed segmentation of inner retinal layers such as retinal nerve fiber layer and ganglion cell layer in patients with RVO[5, 6]. Outer retinal layer (ORL) is formed by photoreceptors, retinal pigment epithelium (RPE) and Bruch's membrane. In a study evaluating relationship between ORL thickness and visual acuity in diabetic macular edema, it was reported that ORL

1- Prof. MD, University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

2- Prof. MD, University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

3- Ophthalmologist, MD, University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

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Correspondence Adress:
Berrak Şekeryapan
University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

Phone: +90 533 369 4183
E-mail: berrakgediz@gmail.com

thickness is a stronger marker for visual acuity than total retinal thickness[7].

In this study, it was aimed to determine ORL thickness by automated segmentation method using spectral domain-OCT (SD-OCT) in patients who received intravitreal injection for macular edema secondary to non-ischemic central vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) and experienced regression in macular edema and to assess relationship between ORL thickness and visual acuity.

MATERIAL AND METHOD

We retrospectively reviewed files of the patients who received intravitreal injection for macular edema secondary to CRVO and BRVO at retina unit of our clinic between January, 2018 and April, 2019 and included patients fulfilling inclusion criteria. The study was approved by local Ethics Committee. The study was conducted in accordance to tenets of Helsinki Declaration.

The study included patients who received loading dose of intravitreal ranibizumab (IVR) forME secondary to unilateral RVO and had no ME in optical coherence tomography (OCT) obtained on month 12. In all patients, best-corrected visual acuity (BCVA) as measured by Snellen chart, intraocular pressure (IOP) values as measured by Goldmann applanation tonometry and central foveal thickness (CFT) at baseline and on month 12, ORL thickness on month 12 and number and types of injections were recorded. Contralateral eyes were employed as controls. The presence of ischemia on fundus fluorescein angiography (FFA), history of previous panretinal or grid argon laser therapy, failure to identify retinal layers on OCT due to cataract and other opacities, choroidal neovascularization or RVO development in control eyes, any previous ocular surgery (other than cataract performed beyond prior 6 months) and presence of diabetic retinopathy were defined as exclusion criteria.

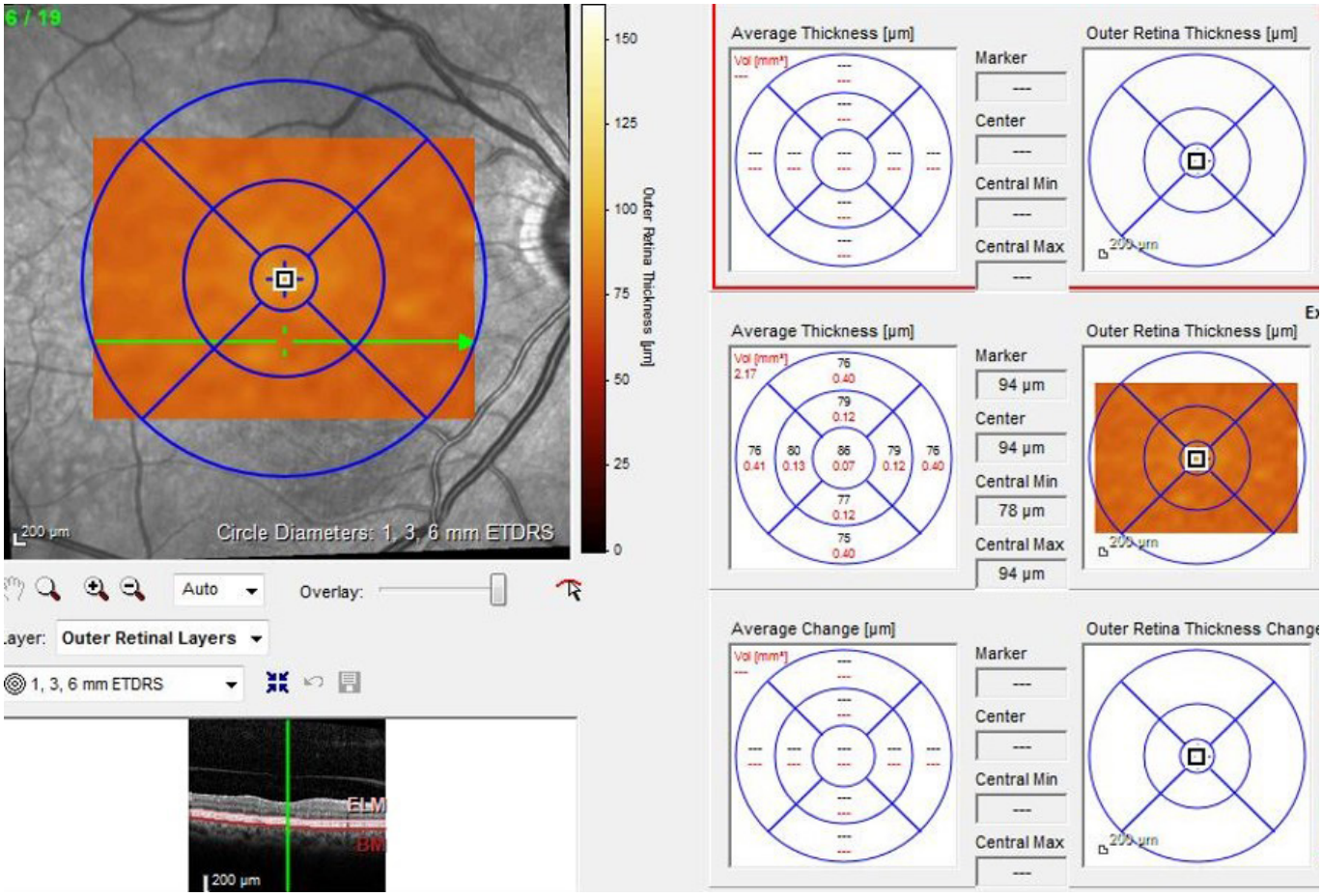
In all patients, thorough ophthalmological examination including SD-OCT was performed at baseline and control visits. Again, FFA was obtained before first injection in all patients whereas it was obtained to assess ischemia when needed in controls. The patients were treated with loading dose of intravitreal ranibizumab (3 monthly injections); followed by PRN intravitreal ranibizumab or dexamethasone (DEX) implant. The repeated treatment was determined based on SD-OCT findings; DEX implant following loading dose was administered to cases with persistent submacular serous retinal detachment.

Outer retinal layer thickness was analyzed using up-to-date version of SD-OCT device (Spektralis OKT, software version 6.5.2; Heidelberg, Germany) which can analyze retinal layers separately in automated manner. Outer retinal layer thickness was measured as distance between external limiting membrane (ELM) and basal membrane. ORL thickness was calculated at areas of standard ETDRS circle corresponding to central (M), interior (superior [S]1, nasal [N]1, inferior [I]1, temporal [T]1) and outer (S2, N2, I2, T2) circles (Figure 1). The ORL thickness was compared between RVO and control groups while the relationship between ORL thickness and BCVA or intravitreal agent was compared within RVO Group. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Wilcoxon test, Mann Whitney U test and Spearman's correlation analysis were used in statistical analyses. A p value<0.05 was considered as statistically significant.

Table 1: *Sectoral comparison of ORL thickness between patients not received DEX implant injection and those received one DEX implant injection.*

ORL		Ozurdex		p[a]
		Not received (n=32)	Received (n=46)	
	M	84.2±4.8 (75-96)	80.0±8.6 (32-95)	**0.001****
	N1	80.7±2.7 (76-86)	79.1±3.7 (73-91)	**0.009****
	N2	78.2±2.6 (73-86)	77.4±3.2 (72-91)	0.128
	T1	79.9±2.9 (74-87)	78.6±3.2 (74-89)	**0.034***
	T2	78.1±2.4 (72-82)	76.8±2.7 (72-84)	**0.026***
	İ1	79.5±2.8 (74-85)	78.8±4.1 (72-96)	0.180
	İ2	77.6±3.3 (73-90)	76.8±3.4 (71-88)	0.169
	S1	79.2±2.4 (71-84)	78.0±3.2 (70-87)	**0.022***
	S2	78.0±2.3 (73-82)	76.7±2.9 (70-84)	**0.018***

*p<0.05; **p<0.01; [a]Mann-Whitney U Test



Picture 1: *ORL thicknesss measured using SD-OCT in automated manner. ORL thickness values at the area corresponding quadrant 9.*

FINDINGS

The study included 156 eyes of 78 patients. Mean age was 62.7 ± 11.4 years (20-84 years). There was CRVO in 23 patients (29.5%) and BRVO in 55 patients (70.5%).

In RVO group, mean BCVA was 0.87±0.46 logMar (0.2-1.8) at baseline and 0.46±0.43 logMar (0-1.8) on month 12 (p <0.01). In RVO group, mean number of injection was 6.05 ± 1.96 (4-11). DEX implant was added to IVR in 59.% of patients. Mean number of injection was 5.5±2.1 (3-8) for IVR and 1.6±0.8 (1-2) for DEX implant. In RVO group, there was no significant in mean number of DEX implant between CRVO and BRVO subgroups (1.6±0.7-1.2±0.8, p>0.05). mean IOP was 16.3 ± 4.7 mmHg (8-25) on month 12.

In RVO group, mean CFT at baseline was 485±23.7 µm (398-654) in patients received DEX implant and 398±34.6 µm (352-467) in patients not received DEX implant (p<0.05). Mean CFT value on month 12 was 265.8±32.5 µm(194-322) in RVO group and 274.1±30.7 µm(223-333) in the control group (p>0.05).

When groups were compared regarding ORL thickness, ORL thickness at M, N1, S1 and S2 segments were significantly lower in RVO (p<0.05, for all). The ORL thickness in M, N1, T1, T2, S1 and S2 segments were significantly lower in eyes received at least one DEX implant compared to eyes received no DEX implant (p

Table 2: *Correlation between mean BCVA (logMar) and ORL thicknesses in RVO patients on month 12*

Outer retinal layer thickness		Visual acuity (LogMAR)	
	M	*-0.305*	***0.007*** **
	N1	-0.199	0.080
	N2	-0.043	0.709
	T1	-0.030	0.792
	T2	0.030	0.797
	I1	-0.090	0.434
	I2	-0.047	0.684
	S1	-0.176	0.122
	S2	0.020	0.860

**p<0.01; Spearman's correlation coefficient

<0.05, all values). There was a significant correlation between the mean BCVA value in the RVO group on month 12 and ORL thickness in segment M (r=-0.305; p <0.01) (Table 2).

DISCUSSION

Based on our results, subfoveal ORL thickness measured after regression of macular edema was lower in RVO patients compared to controls. The extent of reduction in ORL thickness was greater in eyes received at least one DEX implant injection than those received IVR alone. In addition, there was a positive correlation between visual acuity at year one and subfoveal ORL thickness.

Although regression of macular edema, the most common cause of vision loss secondary to RVO, theoretically warrants visual gain, it is not always true in all patients with RVO. In BRAVO study which investigated efficacy of IVR treatment including monthly injection over 6 months, followed by PRN regime, the visual acuity was <20/40 on month 12 in 20% of cases despite regression of macular edema[3]. Although the reason for this variation in visual outcome hasn't been fully elucidated, it is thought that foveal photoreceptor integrity is important. There are studies investigated relationship between final visual acuity and photoreceptor layer integrity in RVO patients. In these studies, it was reported that the integrity of inner and outer photoreceptor segments is determinant for final visual acuity in RVO patients[8-11].

How a retinal circulation disorder, RVO, affects photoreceptor supplied by choroidal circulation? Unlike diabetic maculopathy and age-related macular degeneration, macular edema emerges as an acute vascular event in previously healthy retina. It is thought that blood and exudate containing higher concentrations of lipoproteins leaked from injured retinal vessels lead photoreceptor damage by entering subretinal area[12]. In a study investigated ranibizumab efficacy in BRVO patients with serous macular detachment, it was reported number of injections required was higher while final visual acuity was poorer in eyes with serous macular detachment when compared to those without[13]. In our study, DEX implant was administered to eyes with serous retinal detachment which failed to resolve with IVR therapy and ORL thickness was significantly decreased in eyes underwent DEX implant injection. This finding suggest that the reduction in ORL thickness may be due to toxic effect of subretinal fluid on photoreceptors rather than drug itself.

In recent studies with OCT-Angiography in RVO patients, it was shown that there is a correlation between foveal capillary flow and final visual acuity[14, 15]. In an OCT-Angiography study on 85 patients with regression of macular edema, Wakabayashi et al. reported that deep capillary ischemia was associated with photoreceptor damage and determined final visual acuity.

In our study, ORL thickness was measured as distance between ELM and basal membrane using SD-OCT in automated manner. This value reflects total thickness of photoreceptor layer and RPE layer. In studies on RVO patients, it was shown that RPE integrity as well as photoreceptor integrity is determinant for final visual acuity. Farinha et al. evaluated long-term outcomes in patients underwent IVR injection for RVO and assessed factors determining final visual acuity[16]. Authors suggested that changes in outer retinal layers (ELM, IS/OS band and RPE) significantly altered final visual acuity. In a study by Silva et al., it was shown that capillary ischemia caused by RVO led RPE degeneration at long-term[17].

In conclusion, it should be kept in mind that RVO, leading macular edema and loss of vision at acute period, may also result in permanent loss of vision by causing outer retinal injury at long-term. Aggressive treatment of macular edema and subretinal fluid secondary to RVO may be helpful in preventing outer retinal injury. However, further studies are needed to elucidate pathophysiological processes underlying outer retinal injury.

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