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ORIGINAL ARTICLE

The impact of repeated intravitreal dexamethasone implants on the cornea in patients with macular edema due to retinal vein occlusion

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Abstract

Purpose: This study aimed to assess the impact of repeated 700 µg intravitreal dexamethasone implant (IDI) applications on corneal parameters in patients with macular edema (ME) secondary to retinal vein occlusion (RVO).

Methods: This retrospective pilot study included 62 patients with RVO and 63 control subjects. RVO patients received two or more IDI treatments. Detailed eye examinations, including posterior segment evaluations, corneal topography, and endothelial parameters, were retrieved from the patients' medical records.

Results: The study involved 23 patients with central RVO (CRVO) and 39 with branch RVO (BRVO). Ischemic RVO was present in 52.2% of CRVO and 48.7% of BRVO patients. The mean age of RVO patients was 64.79±10.00 years; for the control group, it was 65.03±9.02 years (p=0.068). Patients received an average of 6.58±3.38 IDI injections. Eyes treated with IDI showed significantly worse best-corrected visual acuity and increased central macular thickness compared to fellow eyes and controls (p<0.001 and p=0.031, respectively). Central corneal thickness was significantly thinner in eyes that received IDI, and anterior corneal depth, anterior and posterior corneal curvature, total high-order corneal aberrations, trefoil, and spherical values were significantly higher (p<0.05). In addition, endothelial cell density was significantly lower, and the mean cell area, minimum cell area, and maximum cell area were higher in the eyes that received IDI (p<0.05).

Conclusion: Repeated IDI injections adversely affect corneal topographic and endothelial parameters in RVO-related ME. These changes were associated with the type and localization of RVO, ischemic status, number of IDI administrations, and lens status.

Keywords: Corneal endothelium; corneal topography; intravitreal dexamethasone implant; retinal vein occlusion; specular microscopy.

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Retinal vein occlusion (RVO) is the second most common retinal vascular disease, presenting as central RVO (CRVO), hemi-central, or branch RVO (BRVO).[1,2] In RVO, increased pressure in the capillary plexus and reduced blood flow lead to ischemia. Secondary to ischemia, vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines increase, causing damage to the blood-retinal barrier and increased vascular permeability. Consequently, macular edema (ME), ischemia, and complications arising from retinal neovascularization develop.[3] In RVO, ME is the most frequent cause of vision loss and is treated with intravitreal corticosteroids and anti-VEGF agents in CRVO and BRVO. Laser therapy may also be used for patients with BRVO.[1]

The intravitreal dexamethasone implant (IDI) (Ozurdex, Allergan Inc., Irvine, California, USA) is a biodegradable, slow-release implant containing 700 µg of preservative-free dexamethasone (DEX). IDI exhibits anti-inflammatory properties and reduces VEGF release.[4,5] Unlike most anti-VEGF treatments, it has a longer duration of effect, lasting 4–6 months, thereby improving patient adherence to treatment.[6]

The SHASTA study demonstrated that IDI is effective and safe in improving visual acuity and central macular thickness (CMT) in patients with RVO receiving multiple IDI treatments for ME. This study reported no adverse effects other than cataract progression and ocular hypertension, which have been observed in other studies.[7] Kwak *et al.*[8] showed that 400 µg IDI had no toxic effects in rabbit corneal, lens, and retinal models. In addition, several studies have investigated the impact of a single application of IDI on the corneal endothelium in patients with RVO.[9,10] Only one study reported no changes in corneal endothelial parameters after an average of 1.5±0.8 (range, 1–3) IDI injections in 12 patients with RVO for ME.[9] However, no study has shown the effect of repeated IDI implant application in ME due to RVO on both corneal topographic and specular microscopic parameters in cases that require much more frequent procedures.

This study aimed to evaluate changes in corneal topographic and endothelial parameters, as measured by specular microscopy, in patients with ME due to RVO who underwent multiple IDI treatments.

Materials and Methods

This retrospective study was conducted between January 2019 and November 2023 at the Department of Ophthalmology of Kartal Dr. Lütfi Kırdar City Hospital. Ethical approval was obtained from the hospital's ethics committee, and the study was conducted in accordance with the principles of the Declaration of Helsinki (Protocol No: 2023/514/250/12). The study included 62 patients aged >18 years who required two or more injections due to ME secondary to RVO and 63 age- and sex-matched healthy controls with minor symptoms such as refractive errors. Exclusion criteria were the presence of any of the following: coexisting neurologic or metabolic disease, corneal disease, infection, endothelial cell count (ECN) <1000/mm^2, retinal disease other than RVO, uveitis, optic nerve disease, contact lens use, previous ocular trauma or surgery except for cataract surgery (patients with a history of complicated cataract surgery or those whose interval between the initial IDI injection and cataract surgery was <6 months were excluded from the study), and intraocular pressure (IOP) that could not be controlled with antiglaucoma treatment.

Patient data were retrieved from the medical records, including sex, laterality, best-corrected visual acuity (BCVA) using Snellen charts, IOP using a Goldmann applanation tonometer, pachymetry, findings of biomicroscopic examination of the anterior and posterior segments, fundus fluorescein angiography (FFA) images, optical coherence tomography (OCT) measurements, corneal topographic and specular microscopic parameters, number of IDI administered, lens status, and any comorbidities.

Measurements of both eyes of patients with RVO, and only one eye of healthy controls, were randomly selected. The retinal nerve fiber layer (RNFL) and CMT were measured using a spectral-domain OCT (Topcon, Japan) device. Before IDI treatment, all patients with RVO underwent evaluation with FFA (Canon CF-1® system, Japan). Patients were classified into two groups: CRVO and BRVO, based on the location of RVO, and further categorized as ischemic or non-ischemic according to the extent of ischemia.

IDI was performed by an experienced ophthalmologist. Following the application of proparacaine hydrochloride (Alcaine 0.5%, Alcon Pharmaceuticals, Couver, Belgium) and disinfection of the eyelid and ocular surface with 5% povidone-iodine, the IDI was injected into the vitreous cavity through the pars plana using a 22-gauge (G) needle with a preloaded implant applicator, positioned 3.5 and 4 mm behind the limbus for phakic and pseudophakic eyes, respectively. After the IDI injection, IOP was measured for each patient, and retinal artery perfusion was evaluated. To prevent infection, all patients were prescribed tobramycin 0.3% (Tobradex, Alcon, UK) 4 times daily for 1 week following IDI. During the follow-up visits, the number of

IDI injections administered due to ME development was recorded for each patient. Detailed information regarding the procedure was provided to all patients before IDI treatment, and written consent was obtained from each participant before treatment.

The corneal topographic parameters of all participants were evaluated by the same experienced technician using the Scheimpflug imaging system (Sirius Topography, CSO, Florence, Italy). To optimize corneal imaging, the participants were instructed to refrain from blinking immediately before each measurement to eliminate ocular surface dryness. Anterior segment parameters, including central corneal thickness (CCT), anterior chamber depth (ACD), corneal volume (CV), anterior and posterior corneal curvature (ACC, PCC, respectively), and the root mean square values of total high-order corneal aberrations (HOAs) within the central 6 mm of the cornea were recorded.

In addition, corneal endothelial cell parameters of all participants were evaluated using the central analysis method by the same experienced technician using non-contact specular microscopy (Tomey EM-4000; Tomey Corporation). This method determined results using the ImageNet software program after manually marking at least 110 neighboring cells. The ECN, endothelial cell density (ECD), mean cell area (MCA), minimum cell area (CAmin), maximum cell area (CAmax), coefficient of variation in cell area (CV%), and hexagonal cell ratio (HEX) were recorded for all participants.

Statistical Analysis

Statistical analyses were performed using R version 2.15.3 (R Core Team, Vienna, Austria, 2013). Data reporting included mean, standard deviation, frequency, and percentage. The normality of the quantitative data was assessed using the Shapiro–Wilk test and graphical examinations. An independent samples *t*-test was used for pairwise comparisons of quantitative variables, showing a normal distribution between the two groups. A one-way analysis of variance was used for comparisons involving more than two groups, and a paired samples *t*-test was used for comparisons within groups. Pearson's Chi-squared test was used to compare categorical data. Pearson's correlation analysis was used to determine the level of relationship between quantitative variables. Fisher's z-transformation was used to compare correlation coefficients. Statistical significance was set at $P<0.05$. An a priori power analysis was conducted using G*Power 3.1 to determine the minimum required sample size. Assuming a medium effect size (Cohen's d=0.5), a significance level of 0.05, and a statistical power of 0.80, the required total sample size was calculated as 102 participants (51 per group).

Results

This study included the eyes of 23 patients with CRVO and 39 patients with BRVO (38.5% inferior BRVO and 61.5% superior BRVO), and randomly selected only one eye of 63 eyes from control patients. According to the FFA results, 52.2% (n=12) of patients with CRVO and 48.7% (n=19; 14 superior, five inferior) of patients with BRVO were diagnosed with ischemic RVO. The mean age of RVO patients was 64.79±10.00 years, compared to 65.03±9.02 years in the control group (P=0.068). Among patients, the mean number of IDI administrations was 6.58±3.38 (2-14). Laser treatment for ischemia was added to the treatment of the 26 patients with RVO. Thirty-eight patients had a history of uncomplicated cataract surgery, 24 patients were phakic, and all control group patients were phakic. Patients whose IOP remained 21 mmHg or higher, despite medical treatment, were excluded from the study. There were no statistically significant differences in age or sex between the patient and control groups. The demographic and clinical characteristics of the study participants are presented in Table 1.

Significant differences in BCVA and CMT were observed upon analysis of the eyes in the IDI group, the fellow eyes, and the control group. BCVA was significantly lower in eyes that received IDI than in fellow eyes and the control group ($P<0.001$, for all comparisons), whereas CMT was significantly higher (P=0.031 and P=0.001, respectively). There were no significant differences between the groups regarding IOP and mean RNFL thickness.

In terms of corneal topographic parameters, CCT was significantly thinner in eyes that received IDI than in fellow eyes and the control group ($P<0.001$). ACD was statistically deeper in eyes that received IDI than in fellow eyes and the control group ($P<0.001$ for all comparisons). ACC and PCC were significantly higher in eyes receiving IDI than in the control group ($P<0.001$ for all). Total HOAs, including trefoil and spherical aberrations, were also significantly higher in eyes that received IDI than in fellow eyes and the control group ($P<0.05$) (Table 2).

In the endothelial parameters, ECN and ECD were significantly lower in eyes that received IDI compared to fellow eyes and the control group ($P<0.001$ for all comparisons). The MCA, CAmin, and CAmax were significantly higher in eyes that received IDI than in fellow eyes and the control group ($P<0.005$, for all comparisons) (Table 2).

Table 1. Demographic and clinic features of all study participants

Parameters	RVO patients (%)	Control group (%)	All participant (%)	*P*
Age (mean±SD)	64.79±10.00	65.03±9.02	64.87±10.67	[a]0.068
Gender				
Female/male, *n* (%)	31 (50)/31(50)	42 (66.7%)/21 (33.3)		[b]0.059
Parameters	**BRVO patients**	**CRVO patients**	**RVO patients**	***P***
IDI number (mean±SD)	5.26±3.19	7.13±3.68	6.58±3.38	[a]0.329
Ischemic status				
Ischemic RVO	19 (48.7)	12 (52.2)	31 (50)	[b]0.793
Non-ischemic RVO	20 (51.3)	11 (47.8)	31 (50)	
Treatment				
IDI	22 (56.4)	14 (60.9)	36 (58.1)	[b]0.731
IDI+LASER	17 (43.6)	9 (39.1)	26 (41.9)	
Laterality of eye				
Right	20 (51.3)	13 (56.5)	33 (53.2)	[b]0.690
Left	19 (48.7)	10 (43.5)	29 (46.8)	

RVO: Retinal vein occlusion, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, IDI: Intravitreal dexamethasone implant, [a]Independent *t*-test, [b]Pearson Chi-square test

Table 2. Comparison of corneal topographic and specular microscopy parameters of participants

Parameters	The eye of RVO[1]	The fellow eye[2]	Control eye[3]	[a]p (1 and 2)	[a]p (1 and 3)	[b]p (2 and 3)
BCVA (logMAR)	0.72±0.45	0.10±0.14	0±0	**<0.001***	**<0.001***	0.285
IOP (mm Hg)	15.48±3.62	14.92±3.08	15.37±3.04	0.173	0.143	0.139
Average RNFL (µm)	100.94±22.71	104.13±12.52	105.92±11.48	0.164	0.126	0.406
CMT (µm)	280.03±68.56	257.80±36.53	247.94±24.41	**0.031***	**0.001***	0.054
CCT (µm)	520.24±37.53	536.13±33.17	542.75±29.47	0.057	**<0.001***	0.054
CV, mm^3	55.69±5.38	57.23±11.64	56.36±2.77	0.302	0.384	0.566
ACD, mm	3.71±0.61	3.42±0.54	3.32±0.42	**<0.001***	**<0.001***	0.224
ACC, D	9.54±7.67	6.23±5.72	4.95±2.04	0.131	**<0.001***	0.235
PCC, D	18.95±13.73	15.90±10.50	11.40±4.98	0.610	**<0.001***	0.545
Total HOAs	0.84±0.61	0.63±0.46	0.58±0.27	**0.034***	**0.003***	0.111
COMA	0.43±0.40	0.40±0.30	0.36±0.18	0.554	0.178	0.307
Trefoil	0.47±0.53	0.30±0.32	0.25±0.17	**0.017***	**0.002***	0.056
Spheric	0.32±0.25	0.25±0.18	0.24±0.10	**0.036***	**0.026***	0.798
ECD (cells/mm^2)	2149.55±463.87	2462.35±342.72	2554.94±277.19	**<0.001***	**<0.001***	0.099
CV (%)	39.90±7.31	38.94±6.61	38.40±4.99	0.384	0.180	0.608
HEX (%)	43.53±6.76	45.58±6.76	45.79±7.65	0.065	0.083	0.869
Mean cell area	490.03±127.17	416.71±89.25	395.84±42.87	**<0.001***	**<0.001***	0.097
Min cell area	116.60±37.75	100.11±27.09	98.90±20.46	**0.008***	**0.002***	0.779
Max cell area	1227.06±459.56	993.71±377.60	929.44±218.55	**0.001***	**<0.001***	0.248
ECN	191.55±57.63	226.53±42.90	230.97±38.60	**<0.001***	**<0.001***	0.544

BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, CMT: Central macular thickness, IOP: Intraocular pressure, CCT: Central corneal thickness, CV: Corneal volume, ACD: Anterior chamber depth, ACC: Anterior corneal curvature, PCC: Posterior corneal curvature, HOA: High order aberration, ECD: Endothelial cell density, CV (%): Coefficient of variation of cell size, HEX: Percentage of hexagonality, D: Diopters, AL: Axial length, ECN: Endothelial number. [a]Independent groups *t*-test, [b]Dependent groups *t*-test, * $P<0.05$

Regarding the differences between eyes that received IDI and fellow eyes in RVO patients, positive correlations were found between the number of IDI injections and BCVA (logMAR) (*r*=0.278, *P*=0.029) as well as CV% (*r*=0.287, *P*=0.024). Negative correlations were observed between the number of IDI injections and both CCT (*r*=–0.259, *P*=0.042) and HEX (*r*=–0.354, *P*=0.005). No statistically significant relationships were found between the number of IDI injections and the other corneal topographic and endothelial parameters (Table 3). According to the relationship between the number of IDI injections and both corneal topographic and endothelial parameters based on lens status, no significant correlations were observed in phakic eyes receiving IDI injections (*P*>0.05). In pseudophakic eyes that received IDI, a positive correlation was found between the number of IDI injections and the CV% (*r*=0.330, *P*=0.043). Negative correlations were found between the number of IDI injections and CCT (*r*=–0.334, *P*=0.040) and HEX (*r*=–0.349, *P*=0.012). There were no statistically significant differences in the correlation levels between the number of IDI injections and other parameters based on lens status (*P*>0.05) (Table 4).

Table 3. Comparison of the differences between the eye with RVO and the fellow eye by the number of IDI

The difference between the RVO eye and the fellow eye	IDI number	
	r	P
BCVA (logMAR)	0.278	**0.029***
IOP (mm Hg)	0.157	0.222
Average RNFL (µm)	0.191	0.137
CMT (µm)	0.047	0.717
CCT (µm)	–0.259	**0.042***
CV, mm^3	–0.032	0.807
ACD, mm	0.158	0.220
ACC, D	–0.132	0.310
PCC, D	–0.184	0.151
Total HOAs	0.165	0.200
COMA	0.008	0.950
Trefoil	–0.172	0.180
Spheric	–0.070	0.589
ECD (cells/mm^2)	–0.146	0.258
CV (%)	0.287	**0.024***
HEX (%)	–0.354	**0.005***
Mean cell area	0.103	0.426
Min cell area	0.082	0.524
Max cell area	0.088	0.495
ECN	–0.190	0.139

IDI: Intravitreal dexamethasone implant, BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, CMT: Central macular thickness, IOP: Intraocular pressure, CCT: Central corneal thickness, CV: Corneal volume, ACD: Anterior chamber depth, ACC: Anterior corneal curvature, PCC: Posterior corneal curvature, HOA: High order aberration, ECD: Endothelial cell density, CV (%): Coefficient of variation of cell size, HEX: Percentage of hexagonality, D: Diopters, AL: Axial length, ECN: Endothelial number. r=Pearson correlation coefficient, **P*<0.05.

Significant differences were found based on the classification of RVO into BRVO (superior and inferior BRVO) and CRVO groups, as well as for BCVA and spherical HOA values, according to the differences between the eyes receiving IDI and the fellow eyes in patients with RVO. The BCVA was significantly lower in the CRVO group than in the BRVO group (*P*=0.012). *Post hoc* evaluations using the Bonferroni test indicated that this difference was significant between the inferior BRVO and CRVO groups (*P*=0.009), whereas no differences were observed among the other groups (*P*>0.05). A statistically significant difference was found for spherical values when compared based on RVO localization (*P*=0.033). *Post hoc* evaluations using the Bonferroni test revealed a significant difference between the superior BRVO and CRVO groups (*P*=0.043), with no differences observed among the other groups (*P*>0.05) (Table 5). Regarding ischemic condition, the ischemic group exhibited significantly lower BCVA and CMT values and higher HOA and COMA values than the non-ischemic group (*P*=0.025, *P*=0.017, *P*=0.043, *P*=0.002, respectively) (Table 6).

Discussion

IDI, the first approved medical treatment for ME secondary to RVO, has shown significant improvement in BCVA and CMT after a single IDI treatment.[11] Studies have demonstrated a similar efficacy and safety profile to that of the initial treatment when IDI is repeated after 6 months, although an increase in cataract cases has been reported.[12] The most common adverse effects observed after IDI include cataracts and increased IOP.[12-14] In this study, we evaluated patients who received multiple IDI treatments for RVO-related ME and observed changes in corneal topographic and specular microscopic parameters associated with the type and localization of RVO, ischemic status, number of IDI treatments, and lens status.

Some studies have investigated corneal topographic changes in eyes that underwent IDI application.[10,15] Güler

Table 4. Comparison of differences between the eye with RVO and the fellow eye according to IDI number and lens status

The difference between the RVO eye and the fellow eye	Phacic		Pseudophacic		Comparing correlation levels	
	IDI number		IDI number			
	r	p	r	*P*	z	*P*
CCT (µm)	–0.040	0.852	–0.334	**0.040***	1.113	>0.05
CV, mm^3	–0.053	0.806	–0.017	0.919	0.131	>0.05
ACD, mm	0.161	0.451	0.053	0.751	0.396	>0.05
ACC, D	0.054	0.805	–0.236	0.155	0.676	>0.05
PCC, D	–0.240	0.259	–0.195	0.240	0.171	>0.05
Total HOAs	0.209	0.326	0.071	0.670	0.511	>0.05
COMA	0.194	0.363	–0.056	0.737	0.915	>0.05
Trefoil	0.022	0.917	–0.225	0.173	0.909	>0.05
Spheric	0.049	0.819	–0.117	0.484	0.603	>0.05
ECD (cells/mm^2)	–0.053	0.805	–0.039	0.816	0.051	>0.05
CV (%)	0.030	0.888	0.330	**0.043***	1.133	>0.05
HEX (%)	–0.183	0.393	–0.349	**0.032***	0.649	>0.05
Mean cell area	0.007	0.972	0.006	0.971	0.004	>0.05
Min cell area	0.266	0.210	–0.033	0.846	1.107	>0.05
Max cell area	–0.096	0.656	0.049	0.769	0.527	>0.05

CCT: Central corneal thickness, CV: Corneal volume, ACD: Anterior chamber depth, ACC: Anterior corneal curvature, PCC: Posterior corneal curvature, HOA: High order aberration, ECD: Endothelial cell density, CV (%): Coefficient of variation of cell size, HEX: Percentage of hexagonality, D: Diopters, AL: Axial length, ECN: Endothelial number. r=Pearson correlation coefficient *$P<0.05$

et al. [10] found no significant change in CCT after a single-dose IDI treatment in patients with RVO. In their study, they attributed this to the fact that the IOP increase that may occur due to the DEX implant does not increase enough to disrupt the endothelial pump function or directly change the mechanical properties of the cornea, which has non-linear viscoelastic tissue properties.[10,16] Bayat *et al*. [15] reported a statistically significant decrease in CCT in the 1st month after single-dose IDI application due to diabetes mellitus (DM)-related ME, linking this change to apoptosis in the corneal endothelium induced by steroids. Nevertheless, other corneal parameters did not show significant changes in these studies.[10,15] In our study, a statistically significant reduction in CCT was observed in eyes that received multiple IDI treatments compared to both fellow eyes and the control group. In addition, significant increases were noted in other corneal topographic parameters, including ACD, ACC, PCC, total HOAs, and spherical and trefoil aberrations. We hypothesized that the thinning observed in CCT and changes in corneal curvature could be attributed to increased corneal DEX concentration due to repeated IDI applications and the pharmacokinetic properties of DEX in the eye. Naageshwaran's study on rabbits' eyes showed that the highest concentration after intracameral DEX injection was in the cornea, followed by the iris-ciliary body and aqueous humor, respectively.[17] This was attributed to the diffusion of lipophilic DEX from the corneal endothelium to the stroma and epithelium. The avascular cornea serves as a reservoir for DEX due to its lack of rapid elimination. Previous studies have also shown that glucocorticoid receptors are present in epithelial, keratocyte, and endothelial cells of the cornea, with low concentrations promoting cell proliferation. In contrast, high doses may induce apoptosis and necrosis in epithelial and endothelial cells.[18] Therefore, the increased DEX concentration may induce apoptosis in corneal cells, which could be the underlying cause of the observed changes in the cornea; however, no histopathological or biochemical verification has been conducted to support this view. Some studies have investigated topographic changes in the cornea after 20-23-25-27G vitrectomy,[19-21] and it was also considered that wound healing and contraction in repeated sclerotomies performed during IDI application may contribute to some changes in corneal curvature. However, no study has yet investigated the simultaneous changes in relation to parameters such as the application

Table 5. Comparison of the difference between the eye with RVO and the fellow eye according to the location of retinal vein occlusion

The difference between the RVO eye and the fellow eye	CRVO (*n*=23)	BRVO (*n*=39)		*P*
		Inferior (*n*=15)	Superior (*n*=24)	
BCVA (logMAR)	0.79±0.46	0.34±0.41	0.64±0.49	**0.012***
IOP (mm Hg)	0.83±3.17	1.19±3.08	0.08±3.48	0.573
Average RNFL (µm)	2.3±24.14	−1.5±9.37	−9.63±12.45	0.059
CMT (µm)	21.04±81.41	−2.75±39.39	19.43±68.11	0.316
CCT (µm)	−1.95±23.4	−8.06±22.67	2.67±22.63	0.216
CV, mm^3	0.96±3.42	−1.5±7.67	−3.78±17.27	0.405
ACD, mm	0.32±0.51	0.37±0.75	0.19±0.45	0.529
ACC, D	2.41±6.27	−0.31±8.17	0.83±6.8	0.281
PCC, D	−0.7±22.34	−2.44±11.07	−0.83±11.51	0.919
Total HOAs	0.2±0.52	0.16±0.75	0±0.49	0.345
COMA	0.03±0.29	0.01±0.48	0.06±0.41	0.917
Trefoil	0.24±0.48	0.18±0.52	0.01±0.29	0.197
Spheric	0.16±0.26	0.12±0.24	0.04±0.25	**0.033***
ECD (cells/mm^2)	338.85±519.99	403.63±701.07	379.25±355.39	0.695
CV (%)	−0.87±10.94	2.88±8.05	1.17±6.32	0.472
HEX (%)	−0.43±6.79	−3.38±11.42	−2.46±8.03	0.606
Mean cell area	82.44±149.83	84.38±211.66	64.04±86.84	0.583
Min cell area	22.64±40.34	19.56±47.56	17.5±34.06	0.320
Max cell area	248.69±433.31	242.38±501.6	149.63±363.52	0.446
ECN	−43.88±96.13	−37.79±71.44	−29.96±51.71	0.806

BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, CMT: Central macular thickness, IOP: Intraocular pressure, CCT: Central corneal thickness, CV: Corneal volume, ACD: Anterior chamber depth, ACC: Anterior corneal curvature, PCC: Posterior corneal curvature, HOA: High order aberration, ECD: Endothelial cell density, CV (%): Coefficient of variation of cell size, HEX: Percentage of hexagonality, D: Diopters, AL: Axial length, ECN: Endothelial number. One-way analysis of variance, *$P<0.05$.

site and injection frequency. Grandinetti *et al*. [19] observed no changes in corneal parameters following 23G and 25G vitrectomy. In contrast, changes in corneal curvature were noted in the 1st month post-20G vitrectomy, returning to pre-operative levels by the 3rd month. Slusher *et al*. [20] specifically noted an increased incidence of astigmatism following repeated pars plana vitrectomy through the same sclerotomy sites.

Studies evaluating its impact on human corneal endothelial cells have also been conducted.[22,23] Jamil *et al*. [22] used specular microscopy to demonstrate that the use of 0.4 mg intracameral DEX did not have a toxic effect on the corneal endothelium. Ilhan *et al*. [9] found no changes in the corneal endothelium of patients with RVO 6 months after IDI treatment for ME. In this study, 19 patients with ME due to RVO received a single-dose IDI application, and 12 patients had an average of 1.5±0.8[1-3] IDI injections. Güler *et al*. [10] found no significant change in corneal endothelial parameters in the 1st month after single-dose IDI in patients with RVO, but observed a significant decrease in ECD in the 3rd month. Bayat *et al*.[15] reported a reduction in ECD in the 1st month after single-dose IDI application in

Table 6. Comparison of the differences between the eye with RVO and the fellow eye according to ischemic status

The difference between the RVO eye and the fellow eye	Ischemic (*n*=31)	Non-ischemic (*n*=31)	*P*
BCVA (logMAR)	0.76±0.47	0.49±0.48	**0.025***
IOP (mm Hg)	0.39±3.32	0.74±3.17	0.669
Average RNFL (µm)	0.16±18.57	−0.55±15.62	0.548
CMT (µm)	4.63±82.62	14±50.33	**0.017***
CCT (µm)	−4.9±16.32	1.32±24.25	0.240
CV, mm^3	−3.29±16.3	0.21±1.68	0.244
ACD, mm	0.32±0.64	0.26±0.47	0.677
ACC, D	2.77±6.99	−0.17±6.33	0.091
PCC, D	−2.74±19.68	0.65±11.57	0.412
Total HOAs	0.03±0.38	−0.26±0.66	**0.043***
COMA	0.18±0.37	0.12±0.34	**0.002***
Trefoil	0.13±0.4	0.1±0.48	0.833
Spheric	0.08±0.24	0.06±0.28	0.773
ECD (cells/mm^2)	−324.26±563.04	−301.35±407.79	0.855
CV (%)	0.39±9.75	1.55±7.62	0.603
HEX (%)	−1.97±10.05	−2.13±7.02	0.942
Mean cell area	73.87±157.94	72.77±116.29	0.975
Min cell area	14.9±46.18	18.06±49.8	0.796
Max cell area	294.68±573.29	172.03±505.08	0.375
ECN	−35.81±59.05	−34.16±71.8	0.922

BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, CMT: Central macular thickness, IOP: Intraocular pressure, CCT: Central corneal thickness, CV: Corneal volume, ACD: Anterior chamber depth, ACC: Anterior corneal curvature, PCC: Posterior corneal curvature, HOA: High order aberration, ECD: Endothelial cell density, CV (%): Coefficient of variation of cell size, HEX: Percentage of hexagonality, D: Diopters, AL: Axial length, ECN: Endothelial number. Independent groups *t*-test, *$P<0.05$

patients with DM, attributing this to the combined effect of DM and IDI. In our study, patients underwent at least two IDI applications; the average number of IDI treatments was 6.58±3.38 (range, 2–14). In cases of ME due to RVO, there was a decrease in ECD and an increase in ACA, CAmin, and CAmax after multiple IDI treatments. We also found a positive correlation between IDI count and CV (%) and a negative correlation between CCT and HEX. These endothelial changes might reflect a response secondary to steroid-induced apoptosis and the toxic effects, or stress associated with repeated IDI applications.

Salvi *et al*. [24] demonstrated that CCT increased by approximately 13.81% in the immediate post-operative period (1 h) following cataract surgery, remained elevated by 6.44% on the first post-operative day compared to pre-operative values, and gradually returned to near-baseline levels by the end of the first post-operative week (0.57% difference). Similarly, Ventura *et al*. [25] reported that CCT returned to pre-operative levels within 3–12 months post-surgery. Following cataract surgery, surgical trauma may lead to increased irregularity in the size, hexagonality, and shape of endothelial cells. However, these changes have been shown in various studies to stabilize over time.[26,27] In our study, all patients had undergone cataract surgery at least 6 months before the first IDI. The observed negative correlations between the number of IDI injections and both CCT and HEX, along with the positive correlation with CV depending on lens status, may be attributed to the facilitated anterior segment penetration of DEX in pseudophakic eyes following repeated IDI administration.

Vural *et al*. [28] reported that CCT was thinner in CRVO patients than in BRVO patients. They associated this with the difference in pathophysiology between CRVO and BRVO. In the subgroups of this study, the spherical aberration value was significantly higher in patients with CRVO compared to those with BRVO. In addition, total HOAs and COMA values were significantly higher, and CMT values were lower in the ischemic group than in the non-ischemic group. We attributed these findings to the increased need for repeated IDI treatments in these patient groups.

This study has certain limitations. First, this was a pilot study conducted with a small sample size due to the limited number of patients available for subgroup analyses. The study was cross-sectional; changes in corneal topographic and endothelial parameters before and after IDI application were not evaluated comparatively, constituting another study limitation. In this context, the changes that may develop secondary to RVO could not be fully distinguished from those potentially induced by IDI.

Studies have demonstrated that repeated IDI application for RVO-related ME improves visual acuity and reduces ME. However, no study has evaluated the effect of repeated IDI application on corneal topographic parameters and endothelial measurements evaluated using specular microscopy. In this study, it was found that multiple IDI applications performed for ME due to RVO may lead to statistically significant changes in corneal parameters. New studies evaluating pre- and post-IDI parameters in a larger patient population will help assess corneal changes that may develop due to repeated IDI application.

Ethics Committee Approval: This study was approved by The

Informed Consent: Written informed consent was obtained from the patient for the preparation of this work.

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Authorship Contributions:

Concept: U.K., S.C., E.K., G.A.; Design: U.K., N.T.G., E.K., G.A.; Supervision: U.K., N.T.G.; Materials: U.K., S.C., E.K., F.I.D.S.; Data Collection and/or Processing: U.K., S.C., E.K., F.I.D.S.; Analysis and/or Interpretation: U.K., N.T.G., S.C., E.K., F.I.D.S., G.A.; Literature Search: U.K., N.T.G., G.A.; Writing: U.K.; Critical Reviews: U.K., N.T.G., G.A.

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