• Clinical Research •

Effect of intravitreal injection of dexamethasone implant on the corneal morphology of young adults with central retinal vein occlusion

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Abstract

● **AIM:** To investigate the effect of intravitreal injection of dexamethasone (DEX) implants on the corneal morphology of young adults with central retinal vein occlusion (CRVO).

● **METHODS:** This was a retrospective study. The information of all patients was collected from the hospital information system. Patients diagnosed with CRVO were included. Corneal morphometric analysis was performed 1, 3, 6, and 12mo after the intravitreal injection of DEX. Corneal endothelial cell density (ECD), hexagonal cell ratio (HEX), and coefficient of variation (CV), central corneal thickness (CCT), anterior chamber depth (ACD), anterior chamber angle (ACA), and anterior chamber volume (ACV) were evaluated.

● **RESULTS:** The mean age of the 80 patients (80 eyes) with CRVO was 33.10±3.26y. The mean disease duration was 4.94±2.12mo. The ECDs before and 1, 3, 6, and 12mo after DEX injection were 2718.22±333.14, 2692.74±324.84, 2577.55±365.27, 2624.30±345.53 cells/mm^2, and 2604.00±321.19 cells/mm^2, respectively. No difference was found in ECD at 1, 6, and 12mo after the injection compared with baselines. The ECD of patients was lower than baseline at three months (P<0.05), whereas the HEX and CV were not statistically significant compared with baseline (P>0.05). At the 12-month follow-up, a trend toward a decrease was observed in the CCT compared with baselines among the enrolled patients, but without significant difference (P>0.05). The parameters of the anterior chamber (ACD, ACA, and ACV) did not change significantly compared with baselines (P>0.05). No significant difference was found in corneal morphology between single and repeated DEX implant injections.

● **CONCLUSION:** In young adults with CRVO, intravitreal injection of DEX can temporarily decrease ECD. However, the remaining corneal endothelial morphological characteristics and anterior chamber parameters are unaffected.

● **KEYWORDS:** cornea; endothelial cell density; central retinal vein occlusion; dexamethasone intravitreal implant; young adults

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INTRODUCTION

Retinal vein occlusion is the second most common retinal vascular disease, followed by diabetic retinopathy. Retinal vein occlusion is subdivided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion. Retinal vein occlusion can cause significant vision loss or secondary macular edema (ME)[1-3]. The underlying causes of CRVO are complex; however, the etiology is associated with inflammatory lesions in individuals less than the age of 40. Nevertheless, the lesions of blood vessels are more common in older individuals[4-5]. A previous study reported that approximately 13% of all RVO patients are young individuals with CRVO[6]. In recent years, young patients with CRVO can be treated with the intravitreal injections of dexamethasone (DEX)[6] intravitreal implant (0.7 mg; Ozurdex®, Allergan, Inc., CA, USA). DEX is a slow-release, water-soluble intraocular drug that contains approximately 700 μg of DEX, exerting an intraocular effect for three to six months[7-9]. Common complications associated with the intravitreal injection of DEX include subconjunctival hemorrhage, glaucoma induction, and cataract formation. However, only a few studies have determined the effect of intravitreal DEX injection on corneal morphology. To determine the clinical relevance of DEX injection in patients with low intracorneal, we aimed to

investigate the effect of intravitreal injection of DEX on the corneal endothelium in young patients with CRVO.

PARTICIPANTS AND METHODS

Ethical Approval The treatment protocol and study design were approved by the Ethics Committee of Xinjiang 474 Hospital (Approval number: 20220302011) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients at study enrollment.

Retrospective case data were obtained from 80 patients (80 eyes) hospitalized at Xinjiang 474 Hospital between July 2019 and August 2020, diagnosed with CRVO. Patient information was extracted from the Hospital Information System (HIS). The cohort comprised 38 males (38 eyes) and 42 females (42 eyes), aged 24 to 38y, with a mean age of 33.10±3.26y and a mean disease duration of 4.94±2.12mo. A thorough examination, including slit lamp microscopy, fundus photography, anterior microscopy, tonometry, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA), was conducted by the same physician, leading to the diagnosis of CRVO with a 12-month follow-up. Inclusion criteria for the group were as follows: 1) age>18y; 2) diagnosis of CRVO confirmed by OCT and FFA; 3) capability to undergo follow-up. Exclusion criteria were as follows: 1) presence of severe refractive interstitial clouding, such as cataract or vitreous hemosiderosis, impacting treatment and examination; 2) glaucoma or high intraocular pressure (IOP) necessitating the use of IOP-lowering or corticosteroid drugs that might increase IOP; 3) corneal endothelial dystrophy, keratitis, and other conditions affecting corneal endothelial count; 4) a history of intraocular surgery.

Following the intravitreal injection of DEX, the conjunctival sac underwent cleaning and disinfection, and the lid was opened using an eyelid opener for all patients. The injection of DEX was administered with a needle inserted 3.5 mm below the temporal region from the corneoscleral rim. Subsequently, postoperative tobramycin DEX eye drops were applied four times daily for three days. All procedures were consistently performed by the same physician.

Corneal endothelial cell density (ECD), hexagonal cell ratio (HEX), and coefficient of variation (CV) were assessed using an SP-3000P corneal endothelium microscope (Topcon SP 3000P noncontact specular microscope; Topcon Corporation, Japan). Two to three consecutive photographs of the central corneal endothelium were obtained, and the most accurate image was selected for morphological observation and automatic computer analysis. All examinations were performed by the same examiner.

The anterior chamber angle (ACA) was measured using Cirrus HD-OCT 5000 (Cirrus HD-OCT 500; Carl Zeiss Meditec, Germany). The scanning procedure involved aligning the center of the scan with the corneoscleral border. Photographs were taken of the atrial angle in two quadrants on the temporal and nasal sides of each eye. For each direction, at least three clear images were captured, and each image underwent three measurements to determine the average value, which was then recorded. All examinations were conducted by the same examiner.

The central corneal thickness (CCT), central anterior chamber depth (ACD), and anterior chamber volume (ACV) were assessed using the Pentacam anterior segment analysis system (Pentacam; Oculus Inc., Germany). Each measurement was taken three times consecutively, and the average value was calculated. All examinations were conducted by the same examiner, ensuring that the imaging quality indicated it was acceptable.

SPSS 20 (SPSS Inc., Chicago, Illinois, USA) were used for statistical analysis. The Kolmogorov-Smirnov test was utilized for all measurements, and the results, conforming to a normal distribution, were expressed as mean±standard deviation (SD). General linear models with repeated-measures analysis of variance (ANOVA) were employed to analyze differences in changes in corneal parameters. $P<0.05$ was considered statistically significant.

RESULTS

Of the 80 patients with CRVO enrolled in this study, 18 patients had associated systemic diseases or ocular diseases, and 62 patients did not have any disease. The specific associated diseases are shown in Table 1.

In total, 80 patients were enrolled in this study and followed up for 12mo. Among them, 38 (47.5%) were male, and 42 (52.5%) were female, with an average age of 33.10±3.26y and a baseline IOP of 15.10±3.20 mm Hg. All patients were diagnosed with CRVO, received intravitrea injections of DEX, and had crystalline eyes. Furthermore, none of the patients underwent intraocular surgery. The baseline and anterior segment characteristics of the patients are shown in Table 2.

For analyzing the corneal endothelial morphology of patients who were administered a single injection, a repeated measures ANOVA test was performed for ECD ($F=3.32$, $P=0.008$). ECD was lower at 1, 3, 6, and 12mo after the injection compared with baseline ($P=0.65$, 0.01, 0.07, and 0.06). Before and after a single injection, the CV and HEX of patients did not change significantly ($P>0.05$). The CCT, ACD, ACA, and ACV in the anterior segment of the eyes were analyzed. As shown in Table 3, although there was a trend of decrease in CCT, it was not statistically significant ($P>0.05$). However, no statistically significant changes were found in ACD, ACA, and ACV.

No statistically significant differences were found in terms of ECD, CV, HEX, and CCT between the single-injection and repeat-injection groups for the analysis of corneal

Table 1 Comparison of associated systemic diseases, and other conditions for patients with CRVO *n* (%)

Condition	CRVO (*n*=80)
Systemic diseases	
Hypertension	1 (1.25%)
Diabetes mellitus	0
Hyperlipidemia	4 (5%)
Sjögren's syndrome	1 (1.25%)
Tuberculous pleurisy	2 (2.5%)
Obesity	1 (1.25%)
Hyperhomocysteinemia	2 (2.5%)
Systemic lupus erythematosus	1 (1.25%)
Other conditions	
Ocular hypertension	2 (2.5%)
Oral contraceptive	3 (3.75%)
Retinal vasculitis	1 (1.25%)
Non-systemic disease/no other conditions	62 (77.5%)

CRVO: Central retinal vein occlusion.

Table 2 The baseline characteristics of the patients mean±SD

Characteristics	*n*=80
Patients	80
Treated eyes	80
Sex, *n*	
Male	38
Female	42
Age, y	33.10±3.26
Laterality, *n*	
Right eye	41
Left eye	39
Duration of CRVO, mo	4.94±2.12
IOP, mm Hg	15.10±3.20
ECD, cells/mm^2	2718.22±333.14
CV, %	31.22±5.53
HEX, %	49.58±6.10
CCT, μm	530.56±31.22
ACD, mm	3.30±0.53
ACA, °	55.21±6.08
ACV, mm^3	198.40±17.22

CRVO: Central retinal vein occlusion; IOP: Intraocular pressure; ECD: Endothelial cell density; CV: Coefficient of variation; HEX: Hexagonality; CCT: Central corneal thickness; ACD: Anterior chamber depth; ACA: Anterior chamber angle; ACV: Anterior chamber volume; SD: Standard deviation.

morphology in patients with repeat injections. At the 12-month postoperative follow-up, no difference was found in ECD, CV, HEX, and CCT between the single injection and repeat injection groups (t=0.45, 0.87, 0.35, and 0.13; P=0.65, 0.38, 0.72, and 0.89, respectively). ECD was decreased in the repeated injection group compared with that in the pre-injection group (t=2.61, P=0.009). However, no significant change was found in terms of CV, HEX, and CCT (t=0.55, 0.38, and 0.51; P=0.64, 0.69, and 0.65, respectively). Anterior segment parameter analysis of patients with single injection and repeated injection is presented in Table 4.

Before surgery, the mean IOP of the patients was 15.10±3.20 mm Hg. Four patients had increased IOP at the 4-week follow-up, with an IOP of 29.3, 28.0, 31, and 32 mm Hg, respectively. The IOP decreased to normal after administering IOP-lowering medications. Moreover, no patient required surgery due to increased IOP.

BCVA (logMAR) of patients before injection was 0.71±0.24, which improved after injection to 0.40±0.19 at the 12-month follow-up (F=17.12, P<0.001). The central macular thickness (CMT) of patients before treatment was 654±178 μm, which significantly decreased after treatment at the 1-, 6-, and 12-month follow-up at 380±155, 225±144, and 156±96 μm, respectively. The difference was statistically significant compared with that before treatment (F=20.12, P<0.001). The changes in BCVA and CMT of patients before and after injection are shown in Table 5.

DISCUSSION

CRVO is a prevalent retinal vascular disease[1-2,10]. Among young people, retinal vasculitis, hypercoagulability, and hemodynamic changes are the most significant risk factors for CRVO. In contrast, hypertension and diabetes are known risk factors for CRVO in elderly patients[11-12]. The onset of CRVO causes glial cell activation and cytokine release in the microenvironment of limited or diffuse ischemia and hypoxia, thereby increasing retinal fluid leakage, impairing clearance, and retinal fluid accumulation at the macula, resulting in the formation of ME[13-14]. The most common cause of vision loss in young patients with CRVO is CRVO-ME. DEX is a water-soluble and biodegradable anti-inflammatory corticosteroid. In recent years, young patients with CRVO have been treated with DEX, which inhibits the synthesis of vascular endothelial growth factor (VEGF), prostaglandins, and inflammatory molecules. The younger the CRVO patient, the longer the interval between the DEX treatments[15-16]. Multiple injections of DEX significantly decreased ME without increasing the risk of infection, suggesting that DEX possesses remarkable safety and clinical efficacy in patients with CRVO. In China, a centralized, randomized, double-blind study reported the same conclusion[17]. Present studies on the vitreous cavity injection of DEX in treating young patients with a primary focus on retinal aspects, including efficacy and safety analysis. Nevertheless, only a few studies have reported the effect of DEX on corneal morphology. It is unknown whether the effect is temporary or permanent and if there is an effect on the parameters of the anterior segment. Furthermore, it is also not known whether the injection of DEX into the vitreous cavity was safe for patients with low corneal endothelium. Therefore,

Table 3 Changes of the corneal parameters mean±SD

Parameters	Baseline	1mo	3mo	6mo	12mo	*F*	*P*
ECD (cells/mm²)	2718.22±333.14	2692.74±324.84	2577.55±365.27	2624.30±345.53	2604.00±321.19	3.32	0.008
CV (%)	31.22±5.53	30.84±6.10	30.92±5.61	29.46±5.37	30.28±4.91	0.18	0.90
HEX (%)	49.58±6.10	48.94±5.90	50.11±5.08	49.78±7.21	49.34±6.81	0.10	1.01
CCT (μm)	530.56±31.22	528.12±29.42	525.92±30.28	527.23±29.84	529.72±30.12	0.49	0.81
ACD (mm)	3.30±0.53	3.30±0.42	3.29±0.45	3.31±0.48	3.30±0.52	0.17	0.98
ACA (°)	55.21±6.08	55.70±6.12	55.06±6.07	54.85±5.98	55.01±6.14	0.15	0.99
ACV (mm³)	198.40±17.22	198.35±16.70	197.15±15.84	196.78±14.90	197.57±16.01	1.45	0.21

ECD: Endothelial cell density; CV: Coefficient of variation; HEX: Hexagonality; CCT: Central corneal thickness; ACD: Anterior chamber depth; ACA: Anterior chamber angle; ACV: Anterior chamber volume; SD: Standard deviation.

Table 4 Changes of the corneal parameters mean±SD

Parameters	Group	Baseline	12mo	*t*	*P*
ECD (cells/mm²)	Single injection	2718.22±333.14	2604.00±321.19	2.38	0.02
	Repeat injection	2732.96±324.50	2614.80±344.21	2.61	0.009
CV (%)	Single injection	31.22±5.53	30.28±4.91	0.63	0.52
	Repeat injection	30.19±5.40	29.87±5.01	0.55	0.64
HEX (%)	Single injection	49.58±6.10	49.34±6.81	0.48	0.62
	Repeat injection	50.12±5.98	49.98±6.14	0.38	0.69
CCT (μm)	Single injection	530.56±31.22	529.72±30.12	0.78	0.43
	Repeat injection	534.11±35.45	533.74±29.88	0.51	0.65

ECD: Endothelial cell density; CV: Coefficient of variation; HEX: Hexagonality; CCT: Central corneal thickness; SD: Standard deviation.

Table 5 Changes of the mean BCVA, CMT evaluated at each time point from intravitreal DEX implant mean±SD

Parameters	Baseline	1mo	6mo	12mo	*F*	*P*
BCVA (logMAR)	0.71±0.24	0.60±0.22	0.49±0.12	0.40±0.19	17.12	<0.001
CMT (μm)	654±178	380±155	225±144	156±96	20.12	<0.001

DEX: Dexamethasone; BCVA: Best corrected visual acuity; CMT: Central macular thickness; SD: Standard deviation.

based on these questions, we performed the present study. In this study, we determined the changes in corneal morphology following the injection of DEX into the vitreous cavity of young patients with CRVO.

Normal corneal endothelium comprises a single layer of cuboidal hexagonal epithelium. Several studies have determined the effects of vitreous cavity injections on corneal morphology in the past, reporting varying conclusions. Malvasi *et al*[18] found no detrimental effects of intravitreal injections of ranibizumab and bevacizumab on the porcine corneal endothelium. Furthermore, Merz *et al*[19] incubated human donor corneas unfit for corneal transplantation with various ranibizumab or bevacizumab concentrations. After four weeks, microscopy of the corneal endothelium showed that neither drug had a cytotoxic effect on the corneal endothelium. Ulutaş[20] reported that intravitreal injections of anti-VEGF agents do not affect corneal endothelium, ocular surface, or anterior segment parameters. Urban *et al*[21] reported that repeated intravitreal injections of ranibizumab or abciximab did not affect CCT but decreased ECD. Havens and Gulati[22] reported that intravitreal injections of DEX lead to a transient decrease in the corneal ECD without affecting cell morphology.

In this study, we examined the corneal morphology in young patients with CRVO at different intervals following the injection of DEX. The ECD values at 1, 3, and 6mo post-DEX injection all exhibited a decrease compared with the preoperative value (P>0.05). Prior studies have indicated that DEX injection may lead to corneal edema and endothelial damage, particularly in cases involving post-vitrectomy, compromised capsular bag integrity post-cataract surgery, aphakic eyes, and IOL implantation in the ciliary sulcus, when the anterior segment of the eye communicates with its posterior segment. Therefore, DEX may migrate to the anterior chamber and damage the cornea[23-24]. All patients in this study were under 40y and had not undergone a vitrectomy. DEX did not migrate to the anterior chamber; the posterior capsule of the lens was intact. Hence, DEX probably did not migrate into the anterior chamber and decreased ECD in this study. Nevertheless, DEX can induce necrosis and apoptosis in corneal endothelial cells at higher concentrations[25]. Therefore, the transient decrease in ECD observed in this study may be attributed to DEX-induced corneal endothelial damage. In our study, no significant changes were found in the other parameters. In a recent study, it has been found that in

the treated eyes, more intravitreal injections were associated with lower ECD, lower HEX, and higher CV[26]. This may result from the age of included participants and more doses of injections. These results indicated that personalized treatment might be considered for patient of different ages.

Increased IOP also decreases ECD; however, DEX is less lipophilic and does not accumulate in the trabecular meshwork as much as the vitreous chamber injection of tretinoin[27]. Therefore, the risk of increased IOP is reduced[28-30]. In this study, four patients showed increased IOP following the injection of DEX. Nevertheless, the ECD of these four eyes did not decrease in the high IOP state. Furthermore, ECD was more damaged when the IOP was more than 40 mm Hg. The IOP of these four patients was increased by less than 40 mm Hg, which returned to normal after the administration of IOP-lowering drugs. Therefore, no significant effect on the ECD was observed[31]. We also determined anterior segment parameters such as ACD, ACA, and ACV. We found no significant effect on ACD, ACA, and ACV in young patients with CRVO after single and repeated injections of DEX into the vitreous cavity.

To conclude, the injection of DEX into the vitreous cavity can cause a transient decrease in ECD; however, it has no significant effect on CV, HEX, ACA, or ACV. In the present study, we analyzed the effect of DEX on corneal morphology and revealed that DEX has a minimal effect on the cornea and that repeated injections are safe. However, the present study has some limitations. Given the retrospective nature of this study, attention should be paid to the reliability of data collection and the limitations of selection bias. Other limitations are the small sample size and the lack of a control group. Meanwhile, all data were collected from one center, which may limit the generalization of our results. In the future, high-quality clinical trials with larger sample sizes and longer follow-up periods are needed to confirm these findings and further elucidate specific clinical situations where treatment may need to be selected.

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