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ARAŞTIRMA / RESEARCH

Efficacy of dexamethasone implant in the treatment of macular edema due to different etiologies

Farklı etyolojilere bağlı maküler ödem tedavisinde deksametazon implantın etkinliği

Emrah Öztürk[1], Burak Esener[2], Abuzer Gündüz[2]

[1]Malatya Training and Research Hospital, Department of Ophthalmology, Malatya, Turkey
[2]Inonu University School of Medicine, Department of Ophthalmology, Malatya, Turkey

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Abstract

Purpose: The aim of this study was to evaluate the effectiveness of intravitreal DEX implant injection in the treatment of macular edema due to four different etiologies.

Materials and Methods: This is a retrospective and case control study. A total of 177 patients who underwent intravitreal DEX implant between 2014 and 2018 for four different etiologies, which are diabetic retinopathy (DR), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and posterior uveitis (PU), were included in the study. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were evaluated in pre-injection, 1st, 3rd, and 6th months post-injection.

Results: Eighty-one patients (45.8%) had DR, 44 (24.9%) had BRVO, 35 (19.8%) had CRVO, and 17 (9.6%) had PU. There was a statistically significant difference in BCVA in the DR, BRVO and PU groups after the injection, but no significant difference was observed in the CRVO group. It is observed that there was a statistically significant decrease in CMT in all groups after the injection. The change in CMT in the 1st month was 153.4 ± 137 μm in the DR group, 161.1 ± 151 μm in the BRVO, 270.5 ± 189 μm in the CRVO and 142.2 ± 174 μm in the PU group.

Conclusion: The intravitreal DEX implant reduces the CMT in patients with macular edema secondary to various etiologies and improves BCVA in patients with macular edema secondary to various etiologies except for patients with CRVO.

Keywords:. Diabetic retinopathy, intravitreal dexamethasone, macular edema, posterior uveitis

Öz

Amaç: Dört farklı etyolojiye bağlı gelişen maküler ödeminin tedavisinde intravitreal DEX implant enjeksiyonunun etkinliğini değerlendirmek.

Gereç ve Yöntem: Bu bir retrospektif vaka kontrol çalışmasıdır. Bu çalışmaya 2014-2018 arasında diyabetik retinopati (DR), branş retinal ven oklüzyonu (BRVO), santral retinal ven oklüzyonu (CRVO) ve posterior üveit (PU) olmak üzere dört farklı etiyolojiden köken alan intravitreal DEX implant uygulaması yapılmış 177 hasta dahil edilmiştir. En iyi düzeltilmiş vizüel aküite (BCVA) ve merkezi makula kalınlığı (CMT) enjeksiyon öncesi, enjeksiyon sonrası 1., 3. ve 6. aylarda değerlendirildi.

Bulgular: Seksen bir hastada DR (%45.8), 44 BRVO (%24.9), 35 CRVO (%19.8) ve 17 PU (%9.6) vardı. Enjeksiyondan sonra DR, BRVO ve PU gruplarında BCVA'da istatistiksel olarak anlamlı bir fark vardı, ancak CRVO grubunda anlamlı bir fark gözlenmedi.. Enjeksiyondan sonra tüm gruplarda CMT'de istatistiksel olarak anlamlı bir azalma olduğu gözlenmiştir. Bir ayda CMT'deki değişiklik DR grubunda 153.4 ± 137 μ m, BRVO'da 161.1 ± 151 μ m, CRVO'da 270.5 ± 189 μ m ve PU grubunda 142.2 ± 174 μ m idi.

Sonuç: İntravitreal DEX implantı, çeşitli etiyolojilere sekonder maküler ödemli hastalarda CMT'yi azalttığı, CRVO olan hastalar hariç çeşitli etiyolojilere ikincil olarak maküler ödemli hastalarda BCVA'yı iyileştirdiği sonucuna varılmıştır.

Anahtar kelimeler: Diyabetik retinopati, intravitreal deksametazon, maküler ödem, posterior üveit

Yazışma Adresi/Address for Correspondence: Dr. Emrah Öztürk, Malatya Training and Research Hospital, Department of Ophthalmology, Malatya, Turkey E-mail: marmaraemrah@hotmail.com
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INTRODUCTION

Macular edema (ME) is an important cause of visual impairment. Macular edema most often appears from retinal diseases such as diabetic retinopathy, retinal vein occlusion (RVO), and uveitis, and commonly causes symptoms of blurred or reduced vision[1]. Corticosteroids have anti-inflammatory, antiangiogenic, and anti permeability effects. They serve as counteract three key pathologic processes involved in the development of ME[2,3]. Direct intravitreal delivery of corticosteroids, which bypasses the blood–retinal barrier, provides a high local drug concentration and decreases the systemic side effects[3].

Dexamethasone (DEX) is a corticosteroid with anti-inflammatory activity up to six-fold higher than triamcinolone, 25-fold higher than fluocinolone acetonide[1]. Injection of DEX into the vitreous humor has a significant disadvantage because the half-life of DEX following intravitreal injection is short (approximately 3 hours), limiting its usefulness[4]. The 0.7 mg intravitreal DEX implant (Ozurdex®, Allergan, Inc., Irvine, CA, USA) is a biodegradable and slow delivery drug[1]. Ozurdex® implant is indicated for non-infectious posterior uveitis such as Behçet's disease, ME due to branch and central retinal vein occlusion, diabetic macular edema and Irvine Gass syndrome [5]. Ozurdex has been approved for the treatment of RVO in 2011, treatment of posterior noninfectious uveitis in 2012 and treatment of adult pseudophakic diabetic ME in 2015[1,6].

Although there are many studies about the effectiveness of DEX implant in the treatment of ME, there are a limited number of studies that evaluate the effectiveness of DEX implant in the treatment of ME that developed due to different etiologies under the same research. The aims of this study were to evaluate the effectiveness of intravitreal DEX implant injection in the treatment of ME due to four different etiologies.

MATERIALS AND METHODS

This is a retrospective study conducted at Inonu University School of Medicine, Department of Ophthalmology. A total of 177 patients who underwent intravitreal DEX implant between 2014 and 2018 for four different etiologies, which are diabetic retinopathy (DR), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and posterior uveitis (PU), were included in the study. A written informed concent was obtained from all patients before the injection. The tenets of Helsinki Declaration were followed and the study protocol was approved by the Inonu University Health Sciences Non-interventional Clinical Research Ethics Committee (Reference number: 2019/7-26).

The inclusion criteria were described as age over 18 years, at least six months of follow-up, and no ocular procedures (e.g., cataract surgery, anti-VEGF injection) except for laser photocoagulation in the six months after DEX implant injection. Patients who had follow-up time less than six months and did not come to routine follow-ups were excluded from the study. A total of 338 patient charts were reviewed between 2014-2018. One hundred sixty-one patients who did not meet the inclusion criteria were excluded from the study. Some patients other than PU group had previously received anti-VEGF treatment, and patients had persistent macular edema.

We analyzed the patients' pre-injection, 1st, 3rd and 6th months post-injection follow-up data, including best-corrected visual acuity (BCVA), slit lamp examination, applanation tonometry for the measurement of intraocular pressure (IOP) and fundus examination. Optical coherence tomography (OCT) images were evaluated in pre-injection, 1st, 3rd and 6th months post-injection in order to determine the central macular thickness (CMT). OCT images were acquired using spectral domain OCT (NIDEK RS-3000, Aichi, Japan). OCT images with a signal strength of 7 or more were used in the analysis. Topical antiglaucomatous treatment was started during the follow-up period in patients with 21 mmHg intraocular pressure and optic nerve findings.

Dexamethasone implant and injection

Ozurdex implant was used in all patients. Ozurdex® (Allergan Inc., Irvine, CA, USA) is a preparation for intravitreal administration in the form of a small rod of 0.46 mm diameter and 6 mm length containing DEX (0.7 mg). This slow release preparation dissolves completely in the vitreous cavity in approximately 6 months. Under local anesthesia in the operating room, 5% povidone-iodine was dropped into the conjunctiva and waited for 3 minutes. Ozurdex ® implant was injected at 3.5 or 4 mm behind the limbus (at the pars plana).

Statistical analysis

SSPS for Windows statistical software (ver. 22.0; IBM Corp., Armonk, NY, USA) was used for the analysis. The results are expressed as means ± standard deviation (SD). Shapiro-Wilk test was used to determine the consistency of continuous variables to normal distribution. In order to investigate the differences between the groups, One Way Anova test, and Kruskal Wallis test were used for quantitative data, and Chi-Square test was used for the qualitative data. The statistical significance of changes in CMT was determined by a Friedman test. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 177 patients who underwent intravitreal DEX implant injection and had at least six months of follow up time included this study. Eighty-one patients (45.8%) had DR, 44 (24.9%) had BRVO, 35 (19.8%) had CRVO, and 17 (9.6%) had PU. There was no statistically significant difference between the groups in terms of gender, baseline lens status, and the eye which the implant was applied ($p = 0.10$, $p=0.37$, $p = 0.16$, respectively). There was a statistically significant difference between the groups in age (p:0.001), (Table 1).

Table 1. Demographic and clinical characteristics of the groups before intravitreal dexamethasone implant injection

Variable		DR group	BRVO group	CRVO group	PU group	P value
Gender (n):	F	46	26	12	8	0.10
	M	35	18	23	9	
Age(year) (mean+sd)		63.5± 9.3	63.8±9.4	63.8±10.2	48.8±15.4	0.001
Eye (n):	R	47	17	16	10	0.165
	L	34	27	19	7	
Lens status:	Phakic	50	33	25	10	0.37
	Pseudophakic	31	11	10	7	

DR: diabetic retinopathy, BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion, PU: posterior uveitis

Table 2. Visual acuities of groups and changes after intravitreal dexamethasone implant injection

(mean+sd)	DR group	BRVO group	CRVO group	PU group	P value
VA in pre-injection (d)	0.16±0.13	0.26±0.24	0.10±0.16	0.14±0.16	0.001
VA in post-injection 1st mo (d)	0.23±0.20	0.38±0.33	0.08±0.13	0.24±0.29	<0.001
VA in post-injection 3rd mo (d)	0.22±0.19	0.35±0.30	0.09±0.17	0.26±0.28	<0.001
VA in post-injection 6th mo (d)	0.18±0.16	0.35±0.30	0.07±0.11	0.25±0.23	0.001
P value	<0.001	<0.001	0.282	<0.001	

DR: diabetic retinopathy, BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion, PU: posterior uveitis, VA: visual acuity, d: decimal, sd: standard deviation

Table 3. Central macular thicknesses of groups and changes after intravitreal dexamethasone implant injection

(mean+sd)	DR group	BRVO group	CRVO group	PU group	P value
CMT in pre-op (μm)	546.2±114.1	539,4±127.1	703,6±205.7	539.5±175.8	0.001
CMT in post-op 1st mo (μm)	392.8±106.2	378.3±100.0	433.9±181.8	397.2±151.3	0.634
CMT in post-op 3rd mo (μm)	436.5±111.8	435.5±143.9	494.3±221.5	439.12±219.3	0.386
CMT in post-op 6th mo (μm)	475.5±129.4	462.6±137.6	534.2±204.3	439.0±195.3	0.108
P value	<0.001	<0.001	<0.001	0.009	

DR: diabetic retinopathy, BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion, PU: posterior uveitis, CMT: central macular thickness, d: decimal, sd: standard deviation

There was a statistically significant difference between groups in BCVA in the pre-injection, 1st, 3rd and 6th months after injection (Figure 1). There was a statistically significant difference in BCVA in the DR, BRVO and PU groups after the injection, but no significant difference was observed in the CRVO group (Table 2). There was a statistically significant difference between groups in CMT in the pre-injection, but no significant

difference in the 1st, 3rd and 6th months after injection. It is observed that there was a statistically significant decrease in CMT in all groups after the injection (Table 3). The change in CMT in the 1st month was 153.4 ± 137 μm in the DR group, 161.1 ± 151 μm in the BRVO, 270.5 ± 189 μm in the CRVO and 142.2 ± 174 μm in the PU group (p = 0.002) (Figure 2). After intravitreal DEX implant injection, peripheral retinal laser photocoagulation was performed in 34 (42%) patients in the DR group, 12 (27.3%) in BRVO, 14 (40%) in CRVO and 1 (5.9%) in PU (p = 0.021). During the follow-up period, IOP increase, which is required medical treatment, was observed in 2 (2.5 %) patients in the DM group, 4 (9.1 %) patients in BRVO group, 6 (17.1 %) patients in CRVO group and 2 (11.8 %) patients in PU group (p=0.027).

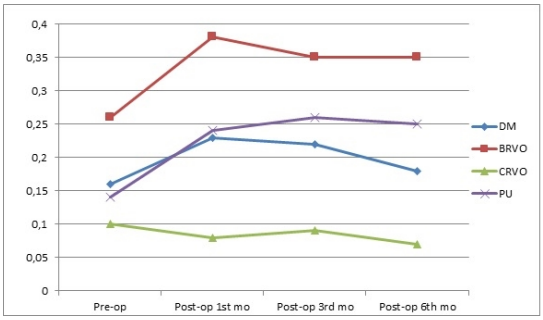

Figure 1. Changes of visual acuity in the groups after intravitreal dexamethasone implant injection

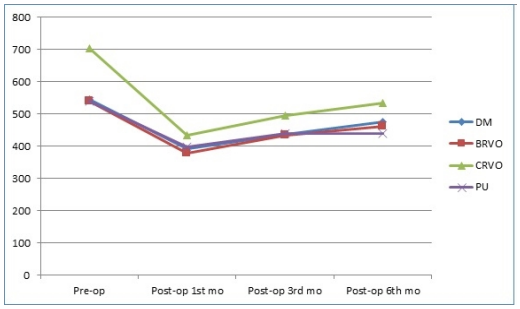

Figure 2. Changes of central macular thickness in the groups after intravitreal dexamethasone implant injection

DISCUSSION

Functional and anatomic improvements after intravitreal DEX implant treatment have been reported in some case series assessing patients with persistent diabetic ME[7,8]. The intravitreal DEX implant provides a reduction in CMT and significant improvement in BCVA[9,10]. In the CHROME study, most of the diabetic eyes had persistent ME despite prior treatment and procedures[1]. Treatment with the intravitreal DEX implant improved BCVA and ME. Compared with baseline, reductions in CMT were statistically significant. Nevertheless, this anatomic improvement is not correlated with a statistically significant improvement in visual acuity for the diabetic ME1. In our study, a statistically significant improvement was observed in both CMT and BCVA after intravitreal DEX implant injection. Unlike the CHROME study, the significant improvement in visual acuity in our study may be due to the fact that the diabetic group consisted of persistent and naive ME patients.

The effectiveness of the intravitreal DEX implant treatment for ME due to branch or central RVO (BRVO, CRVO) was evaluated in two similar, prospective, multicenter, randomized, sham-controlled, 6-month clinical trials. Treatment with a single intravitreal DEX implant injection was provided a significant improvement in BCVA and anatomic outcomes[6,11]. Bezatis et al. reported a retrospective study in which 102 patients with RVO underwent one intravitreal DEX implant treatment, significant improvements in BCVA and reductions in CMT were also observed at every follow-up visit[12]. In our study, RVO patients consisted of two subgroups, BRVO and CRVO. A significant CMT reduction was observed in both groups after the intravitreal DEX implant injection. The BCVA increased significantly in the BRVO group, whereas BCVA remained similar in the CRVO group.

In prospective, multicenter, randomized, sham-controlled, 6-month clinical trial, treatment with a single intravitreal DEX implant for noninfectious uveitis provided a complete resolution of vitreous haze and achieving three or more lines of vision gain throughout the entire study period in most patients[13]. A retrospective study of 27 cases with noninfectious uveitis reported that with repeated intravitreal DEX implant injections, the CMT decreased, and the inflammation resolved, which resulted in improved visual function [14]. In our study, a significant decrease in CMT was observed in the uveitis group after intravitreal DEX implant injection. This reduction

was maximum at 1 month and was relatively maintained at follow-up. On the other hand, an average of two or more lines of vision gain was obtained during the entire study period.

Two previous studies have reported that intravitreal DEX implant treatment provides both functional and anatomic improvements in the treatment of diabetic, retinal vein occlusion, and uveitis-related macular edema in their study, including groups similar to our research[1,15]. Unlike these studies, retinal vein occlusions were evaluated in two different groups as branch and central in our study. In another study, intravitreal DEX implant treatment of eyes with persistent ME secondary to various retinal pathologies provided significant improvements in BCVA and CMT when compared with no treatment[16]. In our study, the anatomic improvement was observed in all groups but the functional improvement was observed in all groups except the CRVO group. The absence of functional improvement in the CRVO group may result from the disease severity or poor prognosis that required more aggressive treatment.

Lam et al. reported that eyes with uveitis demonstrated the most significant gain in BCVA and the greatest decreases in CMT than other etiologies after treatment with the intravitreal DEX implant [1]. In our study, the visual gain was highest in the BRVO and PU group after intravitreal DEX implant injection, whereas no significant change was observed in the CRVO group. The CMT decreased in all groups after intravitreal DEX implant injection. The CMT showed a statistically significant decrease of 28.3 % eyes with diabetes, 29.9% eyes with BRVO, 38.5% eyes with CRVO, and 26.4% eyes with PU at four weeks after the injection. The CMT gradually deteriorated following peak effect. The highest decrease in CMT was observed in the CRVO group, which has the highest macular thickness before injection.

The rate of ocular hypertension that required IOP-lowering medications after treatment with the intravitreal DEX implant observed in this study is 2.5% of eyes with diabetes, 9.1% of eyes with BRVO, 17.1% of eyes with CRVO and 11.8% of eyes with PU. In most of these patients, IOP increase was transient, and glaucoma surgery was not required in any patient. These results are lower than the Phase III trials of the DEX implant whereby the end of the study period, 24% of RVO and 23% of uveitis study eyes needed the use of IOP-lowering medications following treatment with the DEX implant[6,13]. Cataract formation and progression could not be evaluated due to the retrospective nature of the study and the short follow-up period.

Unfortunately, our study has some limitations. Firstly, it's a retrospective study, so adverse events were limited to those reported on the medical charts. Additionally, the groups consisted of persistent and naive macular edema patients. The eyes with RVO were not studied ischemic and nonischemic vein occlusion, which can provide further insight into cases of vein occlusion. Some patients had previously received anti-VEGF treatment. Furthermore, some patients underwent laser photocoagulation co-treatment. Analyses were limited to include data in the patient's medical tables; consequently, some assessments such as evaluation of changes in vitreous haze and cataract could not be assessed.

In conclusion, the intravitreal DEX implant reduces the CMT in patients with ME secondary to various etiologies. The intravitreal DEX implant improves BCVA in patients with ME secondary to various etiologies except for patients with CRVO. Some differences in the efficacy of the intravitreal DEX implant were observed between different etiologies. Further studies are required to clarify the efficacy of the intravitreal DEX implant in ME due to various etiologies.

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