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Original Article/นิพนธ์ต้นฉบับ

Effects of Dexamethasone Implant on Contralateral Central Foveal and Subfoveal Choroidal Thickness in Unilateral Uveitic Macular Edema

Mukaddes Damla Ciftci, MD[1], Mine Esen Baris, MD[2], Suzan Guven, MD[2]

Abstract

Objectives: To investigate the effect of intravitreal dexamethasone implant application on retinal and choroidal thickness of contralateral eye of the patients with uveitic macular edema.

Materials and Methods: This study included 17 patients with non-infectious uveitic macular edema treated with intravitreal dexamethasone implantation. The central foveal thickness (CFT) and subfoveal choroidal thickness (SFCT) measurement taken by swept-source optical coherence tomography were evaluated retrospectively at the pre- and post-injection 1st, 3rd, 6th months, and its relationship with visual acuity was investigated.

Results: Four (23.5%) of the patients had intermediate, 3 (17.6%) had anterior and 10 (58.8%) of them had panuveitis. The mean CFT and SFCT of the eyes with intravitreal implants were 494.3 ± 171.1 and 346.1 ± 68.8 μm respectively. A statistically significant reduction in CFT was observed at the 1st (318.1 ± 65.0, $p < 0.001$), 3rd (314.2 ± 74.2, $p < 0.001$), and 6th (320.6 ± 77.1, $p < 0.001$) months following intravitreal injection. There was a statistically significant decrease of SFCT from the baseline in the 1st month (203.9 ± 62.1 μm, $p < 0.001$), 3rd month (222.1 ± 61.6 μm, $p = 0.002$) and 6th month (224.3 ± 72.6 μm, $p = 0.023$) after the injection. The mean CFT of contralateral eyes was 205.8 ± 55.0 μm before injection and did not change significantly post-injection. The mean SFCT of the contralateral eyes before the injection was 311.2 ± 72.9 μm. Decrease in SFCT of the contralateral eyes at 1st month (288.6 ± 68.5 μm) ($p = 0.02$) was statistically significant. No significant change was observed in visual acuity after injection in contralateral eyes.

Conclusion: Decrease in the choroidal thickness of the contralateral eyes of patients was so limited and temporary that they did not reflect on their visual acuity. Therefore, it was thought that this may be secondary to the small amount of systemic absorption of intravitreal dexamethasone.

Keywords: choroidal thickness, dexamethasone implant, uveitic macular edema

[1]*University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkiye*

[2]*Ege University Faculty of Medicine, Department of Ophthalmology, Izmir, Turkiye*

Introduction

Uveitic macular edema (UME) is a prominent cause of vision loss in patients with uveitis. It is defined as fluid accumulation in the form of cystoid spaces or diffuse retinal thickening within the retinal layers or in the subretinal area due to disruption of the blood-retinal barrier (BRB) because of ocular inflammation.[1] Although it can be observed in all forms of uveitis, it most often accompanies posterior uveitis.[2] Corticosteroids contribute significantly to anatomical and functional recovery in most cases of non-infectious uveitis complicated by macular edema by their immunosuppressive and anti-inflammatory effects.[3] Even though the deterioration of the BRB primarily plays a role in the development of macular edema. Enhanced depth imaging optical coherence tomography; (EDI-OCT) and swept-source optical coherence tomography (SS-OCT) technologies have shown that the choroid also has a place in the pathophysiology and can be used in the evaluation of treatment response, allowing for more detailed imaging of the choroid.[4,5] There are case reports suggesting that the application of dexamethasone intravitreal implant (Ozurdex®; Allergan, Inc., Irvine, CA) may also have an anti-inflammatory effect on the contralateral eye in patients with uveitis.[6] This observation raises the possibility that intravitreally administered dexamethasone may be systemically absorbed. Such a consideration is important both for monitoring the contralateral eye and for assessing potential systemic effects.

The aim of this study is to evaluate and present the effect of intravitreal dexamethasone implant application on retinal and choroidal thickness in the contralateral eye of patients and its relationship with visual acuity in the treatment of UME.

Materials and Methods

A retrospective chart review was performed in the uvea department of Ege University Hospital, Ophthalmology Department. Data from 17 patients who underwent intravitreal dexamethasone implant for non-infectious UME between January 2021 and March 2022 were reviewed. All injections were carried out by two experienced ophthalmic surgeons (MEB and SG). Central foveal thickness (CFT) and subfoveal choroidal thickness (SFCT) measurements of treated and contralateral eyes before injection and 1st, 3rd and 6th months after injection were analyzed retrospectively and their relationship with visual acuity was investigated. CFT and SFCT measurements were evaluated on SS-OCT (DRI-OCT1 Atlantis system, Topcon) images. All participants were scanned by the same experienced OCT technician. SS-OCT imaging was performed using the device's automated macular scan mode, and B-scan segmentation was generated from 50 cross-sectional images. Eyes with low image quality (signal strength <7) were not included in the analysis. All measurements of CFT and SFCT were made by two individual graders (MDC and MEB), who were not masked, at different times using the same image, and the average value was used.

The patients aged ≥18 years who had unilateral macular edema and non-infectious inactive uveitis under systemic immunosuppressive therapy were included in the study. Inactivity criteria were based on laser flare photometry measurements below 7.5 and the absence of cells in the anterior chamber for anterior uveitis. For intermediate and panuveitis, in addition to these, the absence of vitritis and the absence of leakage on fluorescein angiography were accepted as inactivity criteria. In the enrolled patients, persistent UME, despite the absence of clinically detectable

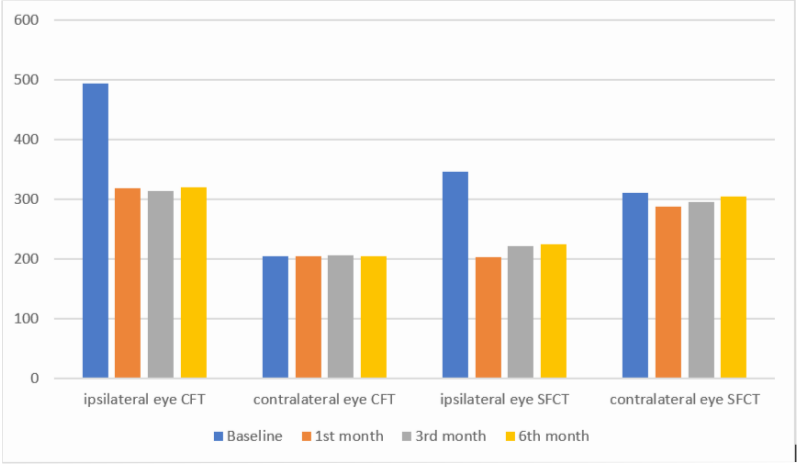
active cellular inflammation, may be attributable to chronic structural or vascular alterations, or to ongoing subclinical inflammatory activity.[7] Consecutive patients who met the aforementioned criteria and underwent intravitreal implantation between January 2021 and March 2022 were included in the study.

Patients with additional systemic pathology or ophthalmological disease that may cause inflammation were excluded from the study. Additionally, patients with systemic comorbidities known to potentially affect the integrity of the blood–retinal barrier as BRB (including diabetes mellitus, hypertension, chronic kidney disease, and other metabolic disorders) were excluded from the study.

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) programs were used in the analysis of the variables. The Shapiro–Wilk test was used to assess the normality of the data distribution. Changes in CMT and SFCT values over time were evaluated using repeated-measures ANOVA within the General Linear Model framework. This study was approved by the Institutional Ethics Review Board of Ege University, Turkey with approval number of 22-12.2T/19 and conducted in agreement with the tenets of the Helsinki Declaration. Each participant signed a written informed consent form for the use of their medical data.

Results

The female/male ratio of 17 patients with a mean age of 56.8 ± 15.1 years was 14/3. The baseline mean CFT and SFCT of the eyes with intravitreal implants were 494.3 ± 171.1 and 346.1 ± 68.8 µm, respectively. A statistically significant reduction in CFT was observed at the 1st (318.1 ± 65.0, $p < 0.001$), 3rd (314.2 ± 74.2, $p < 0.001$), and 6th (320.6 ± 77.1, $p < 0.001$) months following intravitreal injection. There was a statistically significant decrease of SFCT from the baseline in the 1st month (203.9 ± 62.1 µm, $p < 0.001$), 3rd month (222.1 ± 61.6 µm, $p = 0.002$) and 6th month (224.3 ± 72.6 µm, $p = 0.023$) after the injection. The mean CFT of contralateral eyes was 205.8 ± 55.0 µm before injection and did not change significantly at 1st month (204.7 ± 62.2 µm), 3rd month (206.4 ± 57.8 µm) and 6th month (204.5 ± 73.4 µm) ($p = 0.95$) The baseline SFCT of the contralateral eyes before the injection was 311.2 ± 72.9 µm. There was statistically significant decrease in SFCT of the contralateral eyes at 1st month (288.6 ± 68.5 µm) ($p = 0.02$). A mean decrease of 26.82 µm (95% CI: −41.40 to −12.24 µm) in SFCT thickness was observed at post-injection 1st month. SFCT measurements of the contralateral eyes did not change significantly from the baseline value at 3rd month (295.2 ± 77.2 µm) ($p = 0.1$) and 6th month (304.1 ± 77.5 µm) ($p = 0.3$) after injection. Graphic 1 shows change of CFT and SFCT measurements of ipsilateral and contralateral eyes.



Graphic 1 Change of CFT and SFCT measurements of ipsilateral and contralateral eyes at baseline, 1st, 3rd and 6th month after intravitreal Ozurdex® implantation

Intraocular pressure (IOP) was found to be significantly higher at the 1st month (17.1 ± 2.9 mmHg) compared to the baseline (13.7 ± 2.7 mmHg) in the eyes with dexamethasone implant ($p < 0.001$). During the 6-month follow-up, ocular hypertension controlled with anti-glaucomatous eye drops was observed in 3 eyes (17.6%) that had received an intravitreal implant. In contralateral eyes, there was no significant difference in intraocular pressure compared to the baseline (14.4 ± 2.2 mmHg) at 1st month (15.1 ± 2.3 mmHg) ($p = 0.18$). No other adverse events were observed and no serious complications were encountered.

The median best corrected visual acuity (BCVA) before the procedure and at 1st month in the injected eyes were 0.7 (0.2-1.8) and 0.5 (0.1-1.8) logMAR, respectively, with a statistically significant increase ($p = 0.003$). Additionally, the mean decimal BCVA increased from 0.22 ± 0.18 before injection to 0.33 ± 0.25 after injection, representing a mean improvement of 0.11 ± 0.13. This change was statistically significant ($p = 0.003$; 95% CI, 0.041–0.178). No significant correlation was found between visual gains and change in CFT value after injection in eyes treated with dexamethasone implant ($p = 0.49$; r = 0.13). On the other hand, there was no significant difference in the median BCVA of the contralateral eyes before the injection 0.2 (0-1.3) and 1st month after the injection 0.2 (0-1) ($p = 0.85$). The mean decimal BCVA of the contralateral eyes slightly decreased from 0.67 ± 0.34 before injection to 0.67 ± 0.31 after injection, with a mean change of −0.006 ± 0.13. This difference was not statistically significant ($p = 0.85$; 95% CI, −0.074 to 0.062).

Table 1 includes the demographic and clinical characteristics of patients.

Table 1 Clinical and demographic features of the patients

	Baseline Demographic and Clinical Characteristics								Outcome Data			
Patient No.	Age/ Gender	Diagnosis	Laterality of UME	Systemic Treatment	Baseline BCVA (logMAR)		Baseline SFCT (µm)		Post-injection 1st month BCVA (logMAR)		Post-injection SFCT (µm)	
					Ipsilat.	Contralat.	Ipsilat.	Contralat.	Ipsilat.	Contralat.	Ipsilat.	Contralat.
1	53/F	Intermediate uveitis	L	Methotrexate (15 mg/week)	1.8	0	325	299	1.8	0	303	274
2	44/F	Intermediate uveitis	L	Azathioprine (100 mg/day)	0.7	0	480	468	0.5	0	436	400
3	58/F	Panuvetis (Behçet's disease)	L	Adalimumab (40 mg/2 weeks), methylprednisolone (8 mg/day)	0.7	0.2	300	348	0.7	0.2	253	369
4	58/F	Panuveitis	R	Adalimumab (40 mg/2 weeks)	0.2	0.7	369	253	0.1	0.3	354	212
5	72/F	Panuvetis	R	Cyclosporine (100 mg/day)	0.5	0	381	307	0.2	0.1	375	297
6	72/F	Panuvetis	R	Azathioprine (100 mg/day)	0.8	0.2	358	340	0.2	0.1	317	300
7	69/F	Anterior uveitis	L	Methylprednisolone (8 mg/day)	1	1.3	405	378	0.7	0.8	363	298
8	53/F	Intermediate uveitis	L	Methotrexate (15 mg/week)	1.3	0	325	289	1.3	0	307	273
9	57/F	Panuveitis (Behçet's disease)	R	Azathioprine (50 mg/day), methylprednisolone (8 mg/day)	1.3	1	331	323	1	1	323	299
10	68/F	Anterior uveitis	R	Methylprednisolone (8 mg/day)	1.3	0.3	340	285	1	0.3	327	284
11	20/M	Panuveitis (Behçet's disease)	R	Adalimumab (40 mg/2 weeks)	0.3	0	388	316	0.2	0	357	245
12	68/F	Anterior uveitis	L	Methylprednisolone (8mg/day)	1	0.2	320	272	1	0.2	290	272
13	33/F	Panuveitis	R	Adalimumab (40 mg/2 weeks), methotrexate (15 mg/week)	0.7	0.3	389	372	0.5	0.4	318	325
14	44/M	Panuvetis (Behçet's disease)	L	Azathioprine (50 mg/day), olchicine (1 mg/day)	0.4	0	404	394	0.4	0	389	360
15	53/F	Panuvetis (Sarcoidosis)	R	Methotrexate (15 mg/week)	1	0	273	266	0.7	0	226	247
16	67/F	Panuveitis	R	Cyclosporine (100 mg/day)	0.5	0.4	229	244	0.5	0.5	312	240
17	77/M	Intermediate uveitis	L	Azathioprine (100 mg/day)	0.4	0.1	156	137	0.2	0.3	155	140

BCVA: Best-corrected visual acuity, F: female, M: male, Ipsilat.: ipsilateral, Contralat.: contralateral, R: right, L: left, UME: uveitic macular edema

Discussion

In this retrospective study, which included 17 cases of inactive non-infectious uveitis who underwent dexamethasone implant for macular edema, a limited decrease was found in the mean SFCT value in the contralateral eyes at the 1st month after the injection, which was not reflected in the visual acuity. Chang-Lin et al.[8] demonstrated the pharmacokinetic and pharmacodynamic properties of the dexamethasone implant and showed that the drug is present in low concentrations in plasma until the 90th day after intravitreal administration. Especially in the uveitic patients, increased vascular permeability and impaired BRB may increase the systemic absorption of dexamethasone. Habot-Wilner et al.[6] reported bilateral improvement after unilateral intravitreal dexamethasone implantation in a 26-year-old uveitis patient with bilateral vitritis and macular edema. As the patients included in the present study showed no evidence of active cellular inflammation, the effect of the dexamethasone implant was assessed exclusively on UME.

In a retrospective study including the contralateral eyes of 13 patients and 14 control subjects who were administered intravitreal dexamethasone for cystoid macular edema, no significant difference was found between the two groups in terms of central macular thickness and visual acuity.[9] Systemic absorption of intravitreal medications may vary from patient to patient and in different disease groups such as diabetes, retinal vein occlusion and uveitis, depending on the degree of deterioration in the BRB.[10,11]

Gulati et al.[12] reported bilateral good anatomical and functional outcomes in a patient with radiation maculopathy refractory to bevacizumab treatment after intravitreal dexamethasone implant administration. In the case report, it was stated that the patient underwent 4 intravitreal dexamethasone implant applications and after the last injection, there was improvement in vision and a decrease in macular thickness in the contralateral eye. In our study, all the patients that included had only 1 dexamethasone implantation between January 2021 and March 2022. The difference between the number of intravitreal applications may explain the lack of statistically significant change in visual acuity in the contralateral eyes in the present study. On the other hand, the fact that only unilateral macular edema was present in the patients that included the study may also be the reason for this situation.

Significant limitations of the current study are retrospective nature of the chart review design, short follow-up time, absence of systemic dexamethasone plasma level measurements, and limited number of the patients. Furthermore, the lack of a control group or a comparative group with non-uveitic cystoid macular edema constitutes another limitation of the present study. The fact that patients included in our study were under systemic immunosuppressive therapy and did not exhibit active cellular inflammation allowed us to specifically UME; however, the potential influence of immunosuppressive treatment on choroidal and retinal thickness constitutes a potential confounding factor influencing the study outcomes. Choroidal thickness is known to show diurnal variation, and the absence of time-of-day standardization in our measurements constitutes a potential confounding factor that may have affected the study outcomes.[13]

Conclusion

Intravitreal dexamethasone implant is an effective option in the treatment of UME. In this particular study, it provides a decrease in CFT and SFCT values in the eyes that were treated with dexamethasone implant 1, 3 and 6 months after the application. In the contralateral eyes, a decrease in choroidal thickness was observed in the first month after injection and it was thought

that this effect, which was limited and temporary, not reflected on visual acuity, may be secondary to a small amount of systemic absorption of dexamethasone. The transient decrease observed in SFCT can be considered clinically insignificant. Owing to the retrospective design and small sample size, the present results are preliminary and warrant confirmation in larger prospective studies.

Future studies with larger sample sizes and systemic pharmacokinetic monitoring are warranted to better assess the potential effects of the dexamethasone implant on the contralateral eye.

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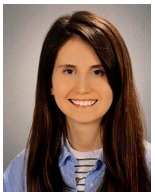
Mukaddes Damla Ciftci, MD[1]


Mine Esen Baris, MD[2]


Suzan Guven, MD[2]

[1]University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkiye
[2]Ege University Faculty of Medicine, Department of Ophthalmology, Izmir, Turkiye

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Correspondence to: **Mukaddes Damla Ciftci, MD**
University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkiye
Phone: 90 543 827 85 05
e-mail: mdamlac@gmail.com