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The Effect of Dexamethasone Implant on Retinal Nerve Fiber Layer and Optic Nerve Cup-to-Disk Ratio in Patients with Diabetic Macular Edema

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ABSTRACT

Aim: The aim of this study is to investigate the effect of single-dose intravitreal Dexamethasone (DEX) implant on peripapillary retinal nerve fiber layer (RNFL) thickness and cup-to-disc (C/D) ratio in patients with diabetic macular edema.

Material and Methods: Peripapillary RNFL thickness measurements and colored fundus photographs were compared before and 6 months after intravitreal DEX implant injection. The cup-to-disc ratios of fundus photographs were calculated using the Image-J program.

Results: Fifty-eight eyes of 43 patients were treated with intravitreal DEX implants. The mean global and sectoral peripapillary RNFL thickness value had a slight thinning over the basal value. The global and nasal thinning was statistically significant (respectively; p=0.021, p=0.036). A small increase in C/D value was observed 6 months after the DEX implant injection; however, these changes were not statistically significant (p=0.285). The intraocular pressure was over 25 mmHg in 17% of the patients and it was controlled by medical treatment.

Conclusion: In this study, in patients with diabetic macular edema, a mild but significant thinning of the global and nasal peripapillary retinal nerve fiber layer was observed 6 months after single-dose intravitreal implant treatment. This reduction did not cause a significant morphological change in the C/D value.

Keywords: *Dexamethasone implant, Diabetic macular edema, Intravitreal injection, Optic disc and nerve fiber layer imaging and analysis, Vascular endothelial growth factor (VEGF)*

Diyabetik Makula Ödemli Hastalarda Deksametazon İmplantının Retina Sinir Lifi Tabakası ve Optik Sinir Çukurluk/Disk Oranı Üzerine Etkisi

ÖZ

Amaç: Bu çalışmanın amacı diyabetik maküla ödemi bulunan hastalarda tek doz intravitreal Deksametazon (DEX) implantının peripapiller retina sinir lifi tabakası (RNFL) kalınlığına ve optik sinir çukurluk/disk (C/D) oranına etkisini araştırmaktır.

Gereç ve Yöntemler: İntravitreal DEX implant enjeksiyonu öncesi peripapiller RNFL kalınlık ölçümleri ve renkli fundus fotoğrafları enjeksiyondan 6 ay sonrası ile karşılaştırıldı. Fundus fotoğraflarının C/D oranları Image-J programı kullanılarak hesaplandı.

Bulgular: Kırk üç hastanın 58 gözüne intravitreal DEX implant enjeksiyonu yapıldı. Ortalama global ve sektörel RNFL kalınlık değerleri bazal değere göre hafif bir incelme gösterdi. Global ve nazal incelme istatistiksel olarak anlamlıydı (sırasıyla; p=0,021, p=0,036). DEX implant enjeksiyonundan 6 ay sonra C/D değerinde hafif bir artış gözlendi, ancak bu artış istatistiksel olarak anlamlı değildi (p=0,258). Hastaların %17'sinde göz içi basıncı 25 mmHg'nin üzerindeydi ve medikal tedavi ile kontrol altına alındı.

Sonuç: Bu çalışmada diyabetik maküla ödemi olan hastalarda tek doz intravitreal DEX tedavisinden 6 ay sonra global ve nazal peripapiller retina sinir lifi tabakasında hafif fakat belirgin bir incelme gözlemlendi. Bu azalma, C/D değerinde önemli bir morfolojik değişikliğe neden olmadı.

Anahtar Sözcükler: *Deksametazon implant, Diyabetik maküler ödem, İntravitreal enjeksiyon, Optik disk ve retina sinir lifi tabakası analizi, Vasküler endotelyal büyüme faktörü*

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INTRODUCTION

Diabetic macular edema (DME) is the most frequent ocular complication of diabetes resulting in irreversible loss of vision if untreated (1). The pathogenesis of DME is multi-factorial. Inflammation plays an important role in this pathogenesis (2). Changes in the vascular endothelial cell tight junction proteins occur with secretion of several inflammatory mediators including Vascular Endothelial Growth Factor (VEGF). These inflammatory mediators lead to deterioration of the blood-retina barrier and DME (3). Steroids inhibit the expression of not only VEGF but also the other inflammatory mediators such as IL-1, IL-6, PEDF, and stabilize the connections between vascular endothelial cells. So they appear to be more effective in DME treatment compared with anti-VEGFs (4). The intravitreal dexamethasone implant (DEX implant; Ozurdex, Allergan, USA) contains 0.7 mg slow-release preservative-free dexamethasone and can retain its effect up to 6 months (5). It has been reported that dexamethasone may have neurodegenerative or neuroprotective effects on retinal nerve fibers (6). It has also been reported that approximately 30% of patients undergoing DEX implantation had intraocular pressure (IOP) elevation exceeding 25 mmHg that required treatment (7). This increase in intraocular pressure is usually controlled by anti-glaucomatous medication. But this increase may be within 1 to 12 weeks after injection. This moment, patients may be in the period they expect to go to the routine control. On the other hand, optic nerve may be more susceptible to damage due to diabetic microvascular complications (8). For these reasons, DEX implant can lead to retinal nerve fiber layer (RNFL) and optic nerve damage by both increasing intraocular pressure and its direct effect on neural tissue during the effective 6-month period.

In this study we investigated RNFL and cup to-disc ratio (C/D) changes in patients with diabetic macular edema treated with single dose intravitreal DEX implant.

MATERIALS and METHODS

The patients diagnosed with Diabetic macular edema and received intravitreal DEX implant therapy were retrospectively studied. The RNFL measurements and cup-to-disc ratios before and 6 months after treatment were recorded. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Patient records were taken from the hospital system retrospectively between the dates of January 2018 - December 2020. Age, gender and complete ophthalmic examination findings including best corrected visual acuity, intraocular pressure, slit lamp examination, fundus examination were recorded. Color fundus photographs, fundus fluorescein angiography (FA) and spectral domain optical coherence tomography (SD-OCT) images of all eyes were examined before and 6 months after intravitreal DEX implant implantation. Patients who had previously received any surgery, intraocular injection or retinal laser photocoagulation were excluded from the study. Patients with proliferative diabetic retinopathy, glaucoma or glaucoma suspicion, optic disc fatigue, optic disc edema, simultaneous ocular diseases such as uveitis and media opacity that blurred of image clarity were excluded from the study.

The injection procedure was as follows: A drop of Proparakain HCl 0.5 % (Alcaine, Alcon, USA) was applied to each eye before injection. The skin around the eye was painted with Povidone-iodine (10%). The lid speculum was used to separate the lids. Afterwards, povidone-iodine (5%) was applied to the intended injection site before injection. Povidone-iodine was left on the conjunctiva surface for 2 minutes and then washed with sterile saline. The upper temporal conjunctiva 3.5-4 mm away from the limbus was dried with a sterile cotton applicator and injection was made in this region. The patients were examined 1 day, 1 week, 1 month, 3 months and 6 months after injection. The other eyes of patients who were not injected in both eyes were included in the study as the control group (n = 24) if they had not received any previous treatment and met the inclusion criteria.

The central and peripapillary RNFL thickness was measured by SD-OCT (Heidelberg Engineering, Heidelberg, Germany). To evaluate the central macular thickness, horizontal cross-sectional images obtained from the fovea center were used. Peripapillary RNFL was measured global and sectoral RNFL thickness in a 360-degree circular scan with 3.45 mm diameter centered on optic disc. Global RNFL thickness was the average of RNFL thickness measurement for this entire circular area. Sectoral areas belonged to 6 parts of this circular area: Superior temporal (TS, 45–90°), superior nasal (NS, 90–135°), nasal (N, 135–225°), inferior nasal (NI, 225–270°), inferior temporal (TI, 270–315°), and temporal (T, 315–45°). At least 3 images of each patient were taken and the best images were recorded. The first obtained images were set as reference and the subsequent images were taken according to this reference. Fundus photographs (Topcon TRC-50DX, Japan) were taken before injections and 6 months after the injections. All of the images were taken by the same expert ophthalmologist (AA). Only images with good quality were recorded. All photos were numbered and cropped from the edges so that only the optical disc would be visible (Figure 1). Then the photos were randomly evaluated. Image J computer

program was used to calculate the disc area and the cup area (9). The outer contour of the disc area was marked and then measured. The cup area was marked at the points where the disc vessels looped and then measured. (Figure 1) All of the measurements were done by the same ophthalmologist (AA) then cup/disc area values were obtained with a simple formula dividing the cup area to disc area.

All statistical analyses were performed using SPSS 19 for Windows (IBM SPSS Statistics, Chicago, IL, USA). Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation, categorical variables as frequency and percent. One-way analysis of variance (ANOVA) with Tukey's test was used to compare multiple groups among themselves. Differences in continuous variables between the baseline dataset and 6th-month dataset was compared by paired samples t-test. $p < 0.05$ was considered statistically significant. Based on studies with similar themes, α=0.05 for the C/D variable, and the effect size value was calculated as a medium-high level effect value (Effect size=0.65). Our sample number, calculated for 80% power according to the two groups, was a total of 78 +4 (spare) sample eyes, and healthy eyes were determined to be taken as control. Power and Sample size analysis was calculated with G power 3.1.9.2 program.

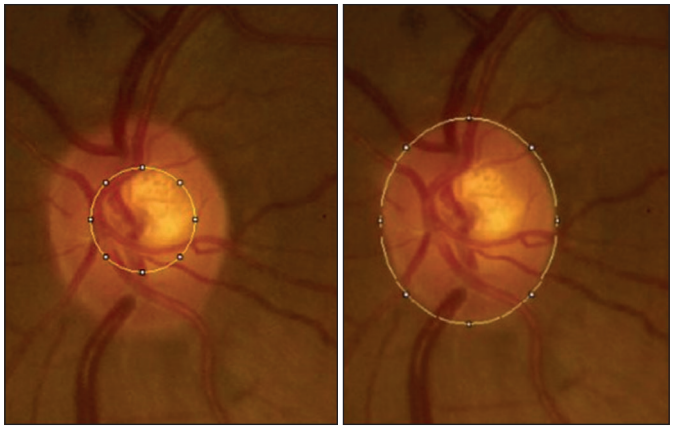

Figure 1: Calculation of optic cup and optical disk area with Image-J computer program.

RESULTS

Single-dose intravitreal DEX implant was applied to 58 eyes of 43 patients with diabetic macular edema. The mean age of the patients was 65.27 ± 8.5 years; 18 (42%) patients were male and 25 (58%) were female. Injection was made to a single eye of 29 patients, and 14 patients' bilaterally. Twenty-four untreated eyes were included in the study as a control group.

At the end of the 6th month, there was a slight decrease in mean RNFL thickness in all quadrants compared to baseline values. When the baseline values of each quadrant were compared with the values of 6th month, there was a significant reduction in global and nasal peripapillary RNFL thickness. (respectively; $p = 0.021$, $p = 0.036$). No significant difference was observed in the other quadrants ($p > 0.05$) (Table 1). When the data of the control group were evaluated, there was no statistically significant difference between the baseline values and the values in the 6th month ($p > 0.05$). RNFL thickness values of the control group are shown in Table 2.

The C/D value of 58 eyes before treatment was 0.273±0.9. The C/D value six months after the treatment was 0.277±0.8. Mean change in C/D value was found to be -0.02±0.03

Table 1: RNFL thicknesses of all quadrants before and 6 months after intravitreal dexamethasone implantation.

RNFL thickness (mm)	TS	NS	N	NI	TI	T	G
Baseline	124.2 ±30.0	115.6 ±32.6	86.4 ±26.3	120.9 ±31.6	134.0 ±28.8	85.3 ±18.5	105.9 ±18.2
6th month	122.2 ±34.8	115.4 ±33.2	81.7 ±25.7	118.1 ±35.0	130.9 ±29.9	84.8 ±18.3	102.6 ±17.6
p	0.446	0.953	**0.021**	0.290	0.261	0.781	**0.036**

Paired Samples t-test; All variables show with mean±Standard Deviation (SD.)
RNFL: Retinal nerve fiber layer, **TS:** Temporal superior, **NS:** Nasal superior, **N:** Nasal, **NI:** Nasal inferior, **TI:** Temporal inferior, **T:** Temporal, **G:** Global.

Table 2: Basal and 6th month RNFL thickness of the control group.

RNFL thickness (mm)	TS	NS	N	NI	TI	T	G
Baseline	115.4 ±22.5	121.5 ±23.7	89.1 ±27.9	148.5 ±33.0	116.9 ±23.1	82.1 ±23.0	106.5 ±16.3
6th month	115.5 ±24.9	122.2 ±25.4	90.4 ±28.9	146.7 ±28.8	117.0 ±23.6	82.3 ±24.0	106.5 ±14.6
p	0.984	0.772	0.476	0.736	0.972	0.937	0.831

Paired Samples t-test; All variables show with mean±Standard Deviation (SD.)
RNFL: Retinal nerve fiber layer, **TS:** Temporal superior, **NS:** Nasal superior, **N:** Nasal, **NI:** Nasal inferior, **TI:** Temporal inferior, **T:** Temporal, **G:** Global.

(95% confidence interval [CI], -0.01 to 0.005). Although there was a minimal increase in C/D value 6 months after DEX injection, this increase was not statistically significant. (p=0.409) (Figure 2). When the C/D values of groups were compared with each other, no statistically significant difference was observed (Table 3).

The mean intraocular pressure of the patients was 16.77±3.3 before the injection, 19.17±3.9 in the first month, 19.68±5.3 in the third month and 16.41±3.3 in the sixth month of injection. There was no significant difference between pre-injection and 6th-month intraocular pressures (p=0.631). During the follow-up period, ten eyes (17%) with intraocular pressures exceeding 25mmHg were treated with anti-glaucomatous treatment. None of the patients had permanent ocular hypertension or required glaucoma surgery. There was no correlation between IOP and RNFL thickness or C/D value.

Cataract progression was observed in 4 cataract eyes. Cataract was observed in 2 eyes without any cataract. None of the eyes with cataract underwent surgery within the follow-up period. Except subconjunctival hemorrhage, none of the patients had complications related to the injection such as vitreous hemorrhage, lens injury, retinal tear/detachment, sterile or infectious endophthalmitis.

Table 3: Compare cap to disc ratios of groups.

Groups	Mean C/D		*P***
	Pre injection	6 month latter	
Treatment group	0.273±0.9	0.277±0.8	0.409
Control group	0.235±0.7	0.246±0.7	0.760
p*	0.285	0.193	

** Paired Samples t-test; * Independent Samples T Test; All variables show with mean±Standard Deviation (SD.)
C/D: Optic nerve cup to disc ratio

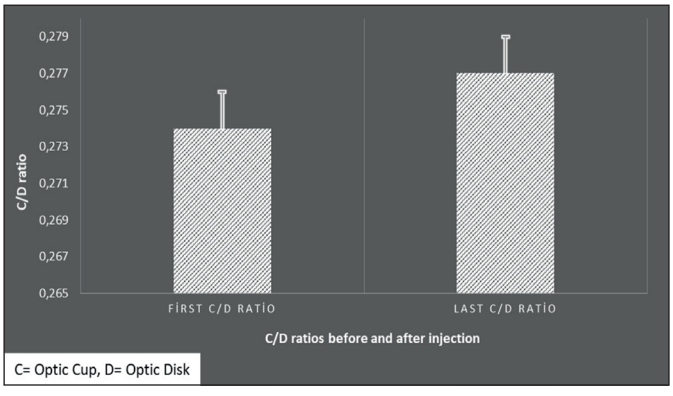

Figure 2: Average optic cup-to-disc ratio change before and six months after application of intravitreal DEX implant application.

DISCUSSION

Nowadays, intravitreal DEX implants have been increasingly used in the treatment of DMO. DEX implant is a biodegradable single use drug delivery system which contains 0.7 mg dexamethasone, a very potent corticosteroid (5). Due to its slow release, the concentration of dexamethasone in the vitreous gradually increases after a single injection, peaks at second months and then decreases, resulting in an effect that can last up to six months (5). It is not exactly known what changes occur in the retinal tissue and retinal nerve fibers that are under continuous steroid exposure for six months. In our study, global and nasal peripapillary RNFL thickness decrease was observed six months after the application of intravitreal DEX implant. Ocular hypertension is a significant complication that occurs after an average of 1-3 months in the use of DEX implant. Lam et al. reported that the intraocular pressure was ≥25mmHg in 26.5% of the patients who had intravitreal DEX implant with the diagnosis of DME (10). Mazzarella et al. evaluated the effect of DEX implant on eyes with ocular hypertension, glaucoma and normal eyes (11). After a single dose DEX implantation intraocular pressure was increased in 59.3% of the patients with ocular hypertension and glaucoma while this ratio was 21.5% in normal eyes. In these previous studies intraocular pressures were generally transient. It can usually be controlled with topical anti-glaucomatous drugs and heals within six months (12). In our study intraocular pressure was ≥25mmHg in ten eyes (17%) and all of the subjects were treated with anti-glaucomatous drugs. The change in RNFL thickness was not significant in 10 patients with elevated intraocular pressure. This may be a statistical finding due to the small number of patients. On the other hand, this change cannot be attributed only to elevated intraocular pressure. Corticosteroids may exhibit both neuroprotective and neurodegenerative effects on nerve cells. The concentration of steroid in the human body is important for neuronal survival. Steroids at physiological level or at a slightly elevated concentration help maintaining neuronal cell integrity. However, steroid levels well below or above normal levels have neurodegenerative effects (13). The neuroprotective effect is thought to be exerted by reducing microglial activity and extracellular glutamate, and increasing the expression of "heat shock proteins", which protect proteins by being secreted under anoxia, hypoxia, and stress (13). Decreased microglial activity also reduces phagocytosis of damaged neurons and production of neurotoxic substances (14).

Vascular Endothelial Growth Factor (VEGF) is an important protein that plays a role in angiogenesis, growth of blood vessels, and increasing vessel permeability. In addition, it

has a direct effect on axonal guidance, neuronal migration and neurite growth (15,16). It has a neuroprotective effect, especially in cases of stress, hypoxia, and oxidative damage. In glaucoma models, VEGF has been shown to have a significant dose-dependent effect on reducing neuronal apoptosis and neural cell death (17). VEGF synthesis is inhibited by corticosteroids (18). Kaderli et al. compared changes in optic disc microvascular parameters before and after treatment of patients who received intravitreal DEX for macular edema secondary to branch retinal vein occlusion, using optical coherence tomography angiography. In this study the mean RNFL thickness at the 2nd and 6th months did not show a statistically significant difference after implantation (19). The long-term effect of the DEX implant on the optic disc is not fully understood. We have found no study examining the effect of Intravitreal DEX implant on RNFL thickness and C/D value in diabetic macular edema treatment. Unlike the monthly intravitreal bevacizumab, ranibizumab or aflibercept treatments, it inhibits all sub-types of VEGF for a relatively long time up to 6 months (20). Long-term inhibition of all VEGF sub-types may further accelerate neural cell damage and ganglion cell loss, resulting in a glaucomatous optic disc appearance. In many studies it has been shown that inhibition of intravitreal VEGF may affect RNFL thickness (21,22). Shin et al. reported a decrease in RNFL thickness in patients with diabetic macular edema after anti-VEGF injection (21). RNFL is more sensitive in eyes with diabetic retinopathy and may be more affected by VEGF inhibition (23). In our study, the reason for the decrease in mean total and nasal RNFL thicknesses may be due to VEGF inhibition, perhaps for 6 months. On the other hand, many studies have reported that there is no change in C/D value and retinal nerve fiber alteration (24,25). But, in these studies, intravitreal anti-VEGF was used for the treatment of macular edema not related to diabetes.

In anti-VEGF treatment, the intraocular pressure is generally increased during the first minutes and then returns to its normal values (26). In the literature we did not come across any studies evaluating the time of the intraocular pressure peak after DEX implantation. However, increase in the intraocular pressure may be seen in the first two weeks after DEX implantation (27). In our practice we examine patients 1 and 4 weeks after the DEX implantation. Possible increase in the intraocular pressure levels during this examination-free period may lead to more damage in RNFL compared with anti-VEGF treatments.

Based on the findings of our study, single dose of intravitreal DEX implant therapy in diabetic macular edema may lead to a reduction in RNFL thickness and a little increases of the optical nerve C/D value. These changes may be due to increased intraocular pressure, neurodegenerative effects of DEX implant and inhibition of VEGF for 6 months. Limitations of our study include being retrospective and low number of patients. We believe that these findings should be confirmed by additional prospective, controlled studies with a large number of subjects.

Acknowledgement

None.

Author Contributions

Numan Küçük conducted ethical and project processes, statistical analysis and constitution of full text. Atilla Alpay conducted admission and treatment of patients, determination of demographic variables and diagnosis of diabetic macular edema.

Conflicts of Interest

There is no conflict of interest among the authors.

Financial Disclosure

No financial support was received.

Ethical Approval

Zonguldak Bülent Ecevit University Clinical Research Ethics Committee approved this study with the meeting number 2022/13.

Peer Review Process

Extremely peer-reviewed and accepted.

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