Comparison of the Effect of Intravitreal Dexamethasone Implant Injection for Retinal Vein Obstruction in Vitrectomized and Nonvitrectomized Eyes

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ABSTRACT

Purpose: This study aimed to compare the effect of dexamethasone (DEX) implant injection on vitrectomized and nonvitrectomized eyes in the treatment of refractory macular edema due to retinal vein obstruction (RVO).

Materials and Methods: Eyes receiving DEX implant treatment for refractory macular edema due to RVO were retrospectively evaluated. In this study, 28 eyes of 28 patients were included, and 12 eyes were previously vitrectomized. The vitrectomized and nonvitrectomized groups were compared at months 0, 1, and 3 in terms of best corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure (IOP).

Results: The BCVA and CMT improved significantly in both groups at month 1 and month 3 compared with the baseline. IOP increase (>20 mmHg) developed in two eyes in the vitrectomized group and in three eyes in the nonvitrectomized group. There was no statistically significant difference between the two groups in terms of IOP, CMT, or BCVA in any of the time points.

Conclusion: In the treatment of refractory macular edema caused by RVO, a single dose of dexamethasone implant leads to comparable anatomical and functional outcomes in both vitrectomized and nonvitrectomized eyes.

Keywords: Dexamethasone, Vitrectomy, Retinal Vein Occlusion, Macular Edema, Intraocular Pressure.

INTRODUCTION

Macular edema due to retinal vein obstruction (RVO) is one of the major causes of vision loss. Factors such as increased hydrostatic pressure, endothelial dysfunction, macular hypoxia, inflammation, and increased permeability in the veins play a role in the formation of macular edema in retinal vein thrombosis (RVT). Treatment options include laser photocoaguation, intravitreal antivascular endothelial growth factor (anti-VEGF) therapy, and intravitreal corticosteroid therapy.[1,2] Intravitreal anti-VEGFs are effective in treating RVO-related macular edema, but frequent injections are required and not all patients respond to the treatment. Because inflammation plays an important role in the etiology of RVO and RVO-related macular edema and as corticosteroids have a broad anti-inflammatory effect, intravitreal corticosteroids are an important treatment option in RVO.[3,4]

Dexamethasone (DEX) intravitreal implant (Ozurdex; Allergan, Inc., Irvine, CA) consists of a biodegradable polylactic acid and glycolic acid copolymer containing micronized DEX. DEX is released from the implant within a few months, turning into lactic acid and glycolic acid, which are metabolized into water and carbon dioxide. Studies on pharmacokinetics and pharmacodynamics of the intravitreal DEX implant show that DEX release from the implant into the vitreoretinal tissues continues for up to 6 months.[5] It has been shown that DEX implant is effective and reliable when anti-VEGF treatment is unsuccessful in eyes with RVO. A single DEX implant and a reinjection after 6 months is safe and improves retinal morphology and visual function.[6-8] Cataracts and increased intraocular pressure (IOP) are the most common side effects of DEX implant therapy.[9]

In vitrectomized eyes, the altered pharmacokinetics

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and pharmacodynamics of intravitreal drugs can lead to reduced therapeutic effects and the need for more frequent injections.[11-15] However, studies on the effectiveness of intravitreal therapies in vitrectomized eyes have reported contradictory results with no consensus.

Therefore, this study aimed to compare the effects and complications of a single dose of intravitreal DEX implant in vitrectomized and nonvitrectomized eyes with macular edema caused by RVO.

MATERIALS AND METHODS

This retrospective clinical trial was conducted in accordance with the principles of the Helsinki Declaration and approved by the Ethics Committee of Ordu University Faculty of Medicine (no: 2022/67, date: 25.03.2022).

The records of 34 patients over the age of 18 years who were followed up for RVO between January 2020 and January 2021 were retrospectively scanned. Of these patients, 28 eyes of 28 patients who received a single dose of intravitreal DEX implant due to refractory macular edema were included in the study. The patients were then divided into two groups: those who underwent pars plana vitrectomy (PPV) (12 eyes) and those who did not (16 eyes). Combined vitrectomy surgeries (phacoemulsification + PPV + endolaser therapy + gas tamponade + ILM peeling) were performed to the eyes in the PPV group due to RVO complications such as vitreous hemorrhage (8 patients), epiretinal membrane (4 patients). In the PPV group, branch retinal vein occlusion (BRVO) was diagnosed in 10 eyes and central retinal vein occlusion (CRVO) was diagnosed in 2 eyes. In the group without PPV, 12 eyes were BRVO and 4 eyes were CRVO. All patients in both groups had received anti-VEGF injections in the past because of RVO-related macular edema. However, the response to treatment was nonexistent to weak. The exclusion criteria in both groups included uncontrolled glaucoma, history of uveitis, permanent macular damage, a follow-up period of <3 months, and receiving intravitreal injection or laser photocoaguation therapy over a period of 3 months before or after DEX injection. In addition, patients who received the DEX implant during PPV and those who received additional treatments, such as anti-VEGF injection and laser photocoagulation, within 3 months of DEX injection were excluded from the study.

A thorough ophthalmological examination was performed on each patient in the 1st and 3rd months before and after DEX implantation. IOP was measured with a noncontact tonometer. Best corrected visual acuity (BCVA) was measured and slit lamp and fundus examinations were performed using indirect ophthalmoscopy. Central macular thickness (CMT) was measured using optical coherence tomography (Cirrus HD-OCT); Carl Zeiss Meditec, Inc., Dublin, CA). BCVA was measured using the Snellen chart and later converted to LogMAR equivalent for statistical analysis.

Intravitreal DEX implant (Ozurdex®, Allergan Inc., Irvine, CA, USA) was injected under topical anesthesia in sterile operating room conditions after cleaning the ocular surface with a 5% povidone iodine solution. All patients were followed up for local and systemic side effects for 3 months. Age, sex, injected eye, PPV surgery, and complications were recorded. Vitrectomized eyes and nonvitrectomized eyes were compared in terms of BCVA, IOP, and CMT measurements in the 1st and 3rd months before and after the injection.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences (V25; SPSS, Inc., Chicago, IL). Mean changes in CMT, IOP, and BCVA measurements were analyzed using paired t-test in both groups. Two-way analysis of variance was used to compare the differences in BCVA and CMT between the vitrectomized and nonvitrectomized groups at the same time points. The data were presented as mean and standard deviation. $P < 0.05$ was accepted as statistically significant in all analyses. The confidence interval was taken as 95%.

RESULTS

Of the patients included in the study, 12 (8 men and 4 women) were in the vitrectomized group and 16 (10 men and 6 women) were in the nonvitrectomized group. All eyes included in the study were pseudophakic. PPV and control group (non-PPV) were matched in terms of key demographic characteristics (Table 1).

After intravitreal DEX injection, significant improvements were seen in BCVA in both groups. The mean baseline BCVA value was 1.39 ± 0.27 LogMAR in the nonvitrectomized group. The mean BCVAs 1 and 3 months after the injection were 0.85 ± 0.18 and 1.05 ± 0.24, respectively. In the vitrectomized group, the mean baseline BCVA was 1.52 ± 0.41. The mean BCVA increased to 1.11 ± 0.49 1 month after the injection and to 1.19 ± 0.43 3 months after the injection. Although there was a decrease in the visual acuity values in the 3rd month of the follow-up in both groups, significant improvements were observed compared with the baseline values ($p = 0.002$ and $p = 0.04$ in the vitrectomized group, respectively; $p = 0.0001$ and $p = 0.0001$ in the nonvitrectomized group, respectively). However, there was no statistically significant difference

Table 1: *General Clinical Characteristics of Patients.*

	PPV group	Control group	P value
Male/Female	8M/4F	10M/6F	0.82
Mean age	59 ± 6.2	58 ± 7.2	0.80
Mean number of anti-VEGF injections	4.5	4.8	0.45
Duration of RVO (months)	10.5 ± 4.9	7.6 ± 3	0.06
Type of retinal vein obstruction			0.30
BRVO	10	12	
CRVO	2	4	
PPV indications (eyes)			
Vitreous hemorrhage	8		
Epiretinal membrane	4		
Mean BCVA (LogMAR) before treatment	1.52 ± 0.41	1.39 ± 0.27	0.46
Mean BCVA 1 month after treatment	1.11 ± 0.49	0.85 ± 0.18	0.42
Mean BCVA 3 months after treatment	1.19 ± 0.43	1.05 ± 0.24	0.34
Mean CMT before treatment	662.25 ± 202.3	666.75 ± 170.81	0.48
Mean CMT 1 month after treatment	380.25 ± 42.35	244.75 ± 74.44	0.09
Mean CMT 3 months after treatment	398.37 ± 100.98	288 ± 62.44	0.09
Mean IOP before treatment	18.2	18	0.43
Mean IOP 1 month after treatment	19.2	21.1	0.18
Mean IOP 3 months after treatment	20.5	21.1	0.42

PPV, Pars plana vitrectomy; RVO, retinal vein occlusion; BRVO, Branch retinal vein occlusion; CRVO, Central macular thickness; BCVA, Best corrected visual acuity; CMT; Central macular thickness, IOP, Intraocular pressure

between the 1st month and the 3rd month BCVA values in both groups. Furthermore, no statistically significant difference was found in the BCVA value between the groups at any of the time points (p = 0.25) (Figure 1).

One month after the DEX implant, statistically significant improvements were seen in CMT in both groups. This significant difference continued until the 3rd month. In the vitrectomy group, the initial CMT value was 662.25 ± 202.30; 1 month after the injection, it was 380.25 ± 42.35

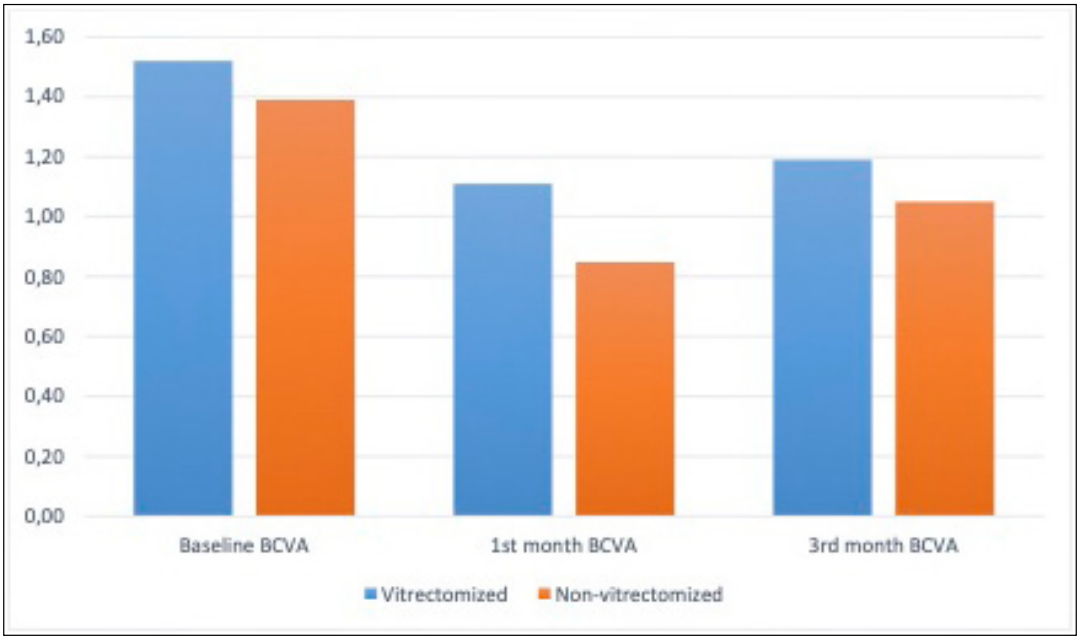

Figure 1: *Change in average best corrected visual acuity in both groups.*

(p = 0.001); and after 3 months, it was 398.37 ± 100.98 (p = 0.01). In eyes without vitrectomy, the initial SMK value was 666.75 ± 170.81; 1 month later, it was 244.75 ± 74.44 (p = 0.001); and 3 months later, it was 288 ± 62.44 (p = 0.01) (Figure 2). No significant difference was found in the CMT values between the groups.

None of the patients included in the study had serious systemic or ocular side effects. IOP increase (>20 mmHg) developed in two eyes in the vitrectomized group and in three eyes in the nonvitrectomized group. Mean IOP increase in the 3rd month was 2.3 mmHg in the vitrectomized group and 3.1 mmHg in the nonvitrectomized group. However, none of these patients developed clinically significant IOP increase (>24 mmHg).

DISCUSSION

The results of the present study showed that single-dose intravitreal DEX implant injection in eyes with RVT-related macular edema has comparable efficacy in vitrectomized and nonvitrectomized eyes. The largest improvement was seen in the 1st month after the injection in both groups. CMT and BCVA declined in the 3rd month, but the improvement persisted compared with the baseline values and was statistically significant in both groups. In the nonvitrectomized group, the decrease in CMT 1 and 3 months after the implantation was more pronounced compared with the vitrectomized group, but this difference was not statistically significant. There was no significant difference between the two groups in terms of CMT or BCVA value at any of the time points.

The most important safety concern related to DEX implant applications is cataract development and IOP increase.[6-9] All the eyes evaluated in the present study were pseudophakic. IOP increased in some of the patients but was controlled in all instances with medical treatment. There was no significant difference between the two groups in terms of baseline, 1st month, and 3rd month IOP values. It has been shown that the increase in IOP is mild and transient in vitrectomized and non-vitrectomized patients who received intravitreal dexamethasone implants to treat macular edema due to different indications. No cumulative effect was observed even in patients receiving multiple doses.[10]

Studies investigating the effect of intravitreal DEX implant in the treatment of resistant macular edema due to retinal vascular diseases showed that the maximum effect occurred within the first 3 months.[16,17] Some patients required reinjection in the 3rd month, whereas this period extended to the 6th month in others.[19] In a study evaluating the early results of dexamethasone implant injection in patients with RVO, significant improvement was achieved in BCVA and CMB at 1 month, and similar results were obtained in both the BRVO and CRVO groups.[18] In the present study, the follow-up period was 3 months and the maximum effect was seen in the 1st month. Three months is relatively short for follow-up, but based on the data obtained from the literature, we are confident that this period is sufficient to observe the effect of the DEX implant.

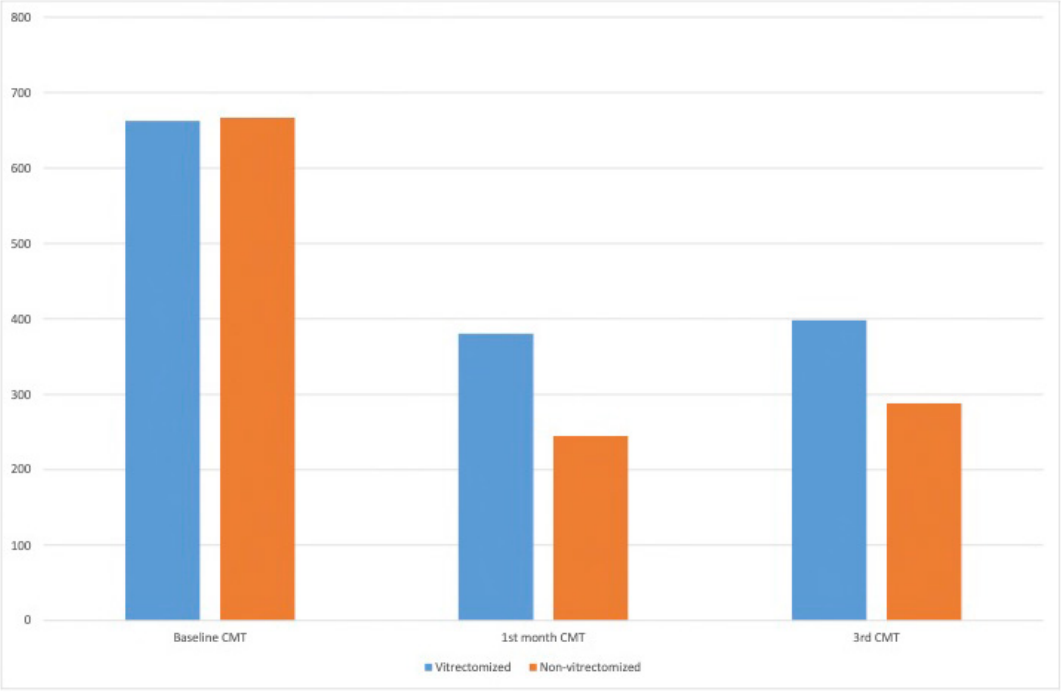

Figure 2: *Average central macular thickness change in both groups.*

The half-life of intravitreal drugs is associated with the presence of vitreous. Most studies investigating the pharmacokinetics of intravitreal drugs in vitrectomized eyes are based on the results of animal experiments. In animal studies evaluating the effects of vitrectomy on the pharmacokinetics and pharmacodynamics of intravitreal drugs, it was argued that the excretion of the drugs could accelerate and the half-life could decrease in vitrectomized eyes.[13,15,19] Accordingly, the authors suggested that the dose and frequency of intravitreal drug applications may vary in vitrectomized eyes. In a study investigating the pharmacokinetics of intravitreal anti-VEGF injections in vitrectomized and non-vitrectomized macaque eyes, the half-life of ranibizumab and aflibercept was found to be lower in vitrectomized eyes compared to non-vitrectomized eyes.[27] In another study in rabbit eyes, intravitreal triamcinolone clearance was found to be faster in vitrectomized eyes.[10] Although animal studies give some insight into the pharmacokinetics of drugs, they are not definitive due to differences in vitreous volume between the human and animal eyes and the absence of a pseudophakia pattern.[28] Contradictory results were reported in studies comparing the effect of intravitreal anti-VEGFs in vitrectomized and nonvitrectomized human eyes. Koyanagi et al. found that ranibizumab treatment for diabetic macular edema had similar effects on vitrectomized and nonvitrectomized eyes.[21] In another study, nonvitrectomized eyes were found to be associated with better anatomical and functional outcomes after intravitreal anti-VEGF treatment in diabetic macular edema compared with vitrectomized eyes.[22] In contrast, studies with DEX implants reported consistent results. The efficacy of intravitreal dexamethasone implant injection in eyes with anti-VEGF-resistant diabetic macular edema was compared in vitrectomized and non-vitrectomized eyes, and no significant difference was found between the 2 groups at any time point during the 6-month follow-up.[23,24] Ozdemir et al. found that a single injection of dexamethasone for 6 months improved visual acuity and reduced central retinal thickness in most eyes.[29] There are a limited number of studies investigating the effect of intravitreal drugs in eyes with retinal vein occlusion who have undergone vitrectomy surgery. Houben et al. evaluated the effect of previous vitrectomy on the efficacy of multiple dexamethasone implants in the treatment of refractory macular edema associated with RVO, and obtained similar anatomical and functional responses in vitrectomized and non-vitrectomized eyes. A significant decrease in CMT was seen 3 months after injection, and in most patients this effect lasted up to 6 months. It was observed that the improvement in CMT was maintained with repeated dexamethasone injections.[26] In our study, the improvement in CMT at 1 and 3 months after injection was more striking in non-vitrectomized eyes. These findings may be due to the shorter time from diagnosis to dexamethasone injection in non-vitrectomized eyes. In another retrospective comparative study, similar visual acuity results and improvement in macular edema were found in vitrectomized eyes when dexamethasone implant was used in the treatment of macular edema secondary to CRVO.[25]

There are certain limitations in the present study. The study was designed retrospectively and did not include randomization. Furthermore, the sample size was small, and the follow-up period was relatively short. The results during the 3 months of follow-up after the injection were similar in both groups. However, we do not have any data on the effects after the 3rd month. In addition, because a single-dose DEX implant was used in the present study, the results obtained do not necessarily reflect the results of multiple injections. Furthermore, the fact that the RVO duration was longer in the PPV group than in the control group might have caused selection bias. Because all the patients included in the present study were pseudophakic, we did not have the opportunity to evaluate the development of cataracts, which is one of the important risks of DEX implant. On the other hand, it was important that both the ppv group and the control group were pseudophakic in terms of the formation of homogeneous groups. In addition, all the eyes included in the study being pseudophakic, the possible effect of the condition of the lens on the outcome of the treatment was ruled out. Also, the fact that both groups were similar in terms of RVO type, received a similar number of anti-VEGF treatments before DEX implant treatment, and that no laser photocoaguation was previously performed on the patients are the strengths of the present study.

In conclusion, in the treatment of refractory macular edema caused by RVO, a single dose of DEX implant leads to comparable anatomical and functional outcomes in vitrectomized and nonvitrectomized eyes. There was no significant difference between the two groups in terms of IOP increase, which is one of the most important side effects of intravitreal DEX implant treatment. Prospective randomized controlled trials are needed to further evaluate the effect of multiple DEX implant therapy on vitrectomized eyes in retinal vascular diseases.

Conflict of interest: There is no potential conflict of interest relevant to this study.

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