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Original Article

Evaluation of the Effect of Intravitreal Dexamethasone (Ozurdex®) Implant on Intraocular Pressure in Vitrectomized and Non-Vitrectomized Eyes with Macular Edema

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Abstract

Objectives: This study aimed to retrospectively evaluate the intraocular pressure (IOP) change in vitrectomized and non-vitrectomized patients receiving 0.7 mg intravitreal dexamethasone implant to treat macular edema due to different indications.

Materials and Methods: The patients' diagnoses, IOP values before receiving the intravitreal dexamethasone implant and in follow-up examinations at 1-3 days, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months after implantation, pachymetry values, medications used, and history of vitrectomy surgery were recorded.

Results: A total of 134 eyes of 112 patients between 46 and 85 years of age who received intravitreal dexamethasone implants were evaluated. Seventeen eyes (12.7%) were vitrectomized and 117 (87.3%) were not vitrectomized. In non-vitrectomized eyes, the mean IOP was 14.01±2.36 mmHg before and 14.8±2.96 at 1-3 days, 16.71±3.97 at 1 month, 17.88±5.27 at 2 months, 15.54±3.35 at 3 months, 15.1±3.24 at 6 months, and 14.61±3.71 mmHg at 12 months after receiving the first dose. In this group, the increases in mean IOP at 1-3 days, 1 month, 2 months, and 3 months were significant compared to the mean IOP before the first dose ($p<0.05$). In vitrectomized eyes, only the increase in mean IOP at 6 months was significant compared to the mean IOP before the first dose ($p<0.05$). Twenty-three of the 134 eyes (17.2%) were prescribed 1-3 medications due to IOP elevation (one drug for 73.9%, two drugs for 17.4%, and three drugs for 8.7% of these eyes).

Conclusion: The IOP increase that occurs as a side effect of intravitreal dexamethasone administration is generally mild and temporary in both vitrectomized and non-vitrectomized eyes, regardless of indication. There was no cumulative effect in patients who received two or three doses.

Keywords: Intravitreal, dexamethasone, glaucoma, macular edema

Introduction

Corticosteroids are used topically, periocularly, or intravitreally in the treatment of many inflammatory and autoimmune ocular diseases. One of the complications of intravitreal steroid administration is elevated intraocular pressure (IOP). Ocular hypertension has been defined as an IOP ≥25 mmHg or ≥10 mmHg above baseline.[1] Ocular hypertension can be a direct result of increased intraocular volume or may occur due to the adverse effect of steroids on aqueous drainage weeks or months after administration.[2] Risk factors include glaucoma, young age, development of ocular hypertension after a previous injection, uveitis, and high-dose steroid use. Detecting secondary ocular hypertension is essential because most cases are asymptomatic and it can lead to permanent vision loss if left untreated.

The dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) is injected into the vitreous cavity with a 22-gauge needle, contains 0.7 mg dexamethasone, and releases corticosteroid for

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an average of 6 months.[3] In animal studies it was observed that the intravitreal dexamethasone (IVD) concentration peaked after 2 months and decreased rapidly between 2 and 3 months. After 6 months, the intravitreal concentration reaches an undetectable level.[4]

In this study, we evaluated the IOP changes in vitrectomized and non-vitrectomized eyes treated with 0.7 mg IVD implant due to macular edema for different indications.

Materials and Methods

Ethical approval for the study was obtained from the ethics committee of the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital. In this retrospective, single-center clinical study, we evaluated patients between 20 and 85 years of age who were followed up in the retina unit of our hospital's ophthalmology clinic and underwent IVD implantation in one or both eyes due to macular edema of varying etiology between April 2016 and January 2018. Each intravitreal implant was administered under topical anesthesia using a 22-gauge injector. Exclusion criteria were as follows: presence of known glaucoma (primary open-angle glaucoma, uveitic glaucoma, neovascular glaucoma, angle closure glaucoma); receiving any intravitreal injection within 3 months before receiving the first IVD implant; an IOP higher than 21 mmHg before implantation; use of systemic or topical corticosteroids; receiving subTenon or subconjunctival steroid; presence of uncontrolled diabetes mellitus with >10% HbA1c; presence of iris neovascularization or intravitreal hemorrhage; having undergone laser therapy, additional ocular surgery, or trauma during follow-up; history of ocular cytomegalovirus or herpes infection; and presence of infectious uveitis or retinitis. Each patient's diagnosis, age, IOP values before IVD implantation, and IOP and pachymetry values measured with a tonometer/pachymeter (Canon TX-20P, Canon Medical Systems, Japan) between 8:30 and 11:00 AM at 1-3 days, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months after implantation were recorded. In addition, history of pars plana vitrectomy and indication (e.g., diabetic retinopathy, retinal detachment, macular hole, intravitreal hemorrhage), need for IOP-lowering medication after IVD implantation, and the number of medications initiated were noted. The patients included in the study were divided into two main groups, vitrectomized and non-vitrectomized. Non-vitrectomized patients were divided into subgroups according to etiology: diabetic macular edema (DME), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), non-infectious uveitis, and macular edema associated with retinitis pigmentosa (RP). All vitrectomized patients had completed panretinal photocoagulation treatment for proliferative diabetic retinopathy (DRP) and did not receive silicone oil or gas.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA) software package. The Shapiro-Wilk test was used to test whether the study data were normally distributed. In addition to descriptive statistical methods (mean, standard deviation, frequency), Mann-Whitney U test was used to compare quantitative data between two groups for parameters that did not show normal distribution. Within-group comparisons were performed with paired samples t-test for normally distributed parameters and Wilcoxon signed rank test for non-normally distributed parameters. Pearson correlation analysis was used to examine relationships between normally distributed parameters. Statistical significance was accepted at $p<0.05$.

Results

A total of 134 eyes of 112 patients between the ages of 46 and 85 years who underwent IVD implantation in the retina unit of our clinic between April 2016 and January 2018 were included in the study. Of these, 17 eyes (12.7%) were vitrectomized and 117 (87.3%) were non-vitrectomized. In the non-vitrectomized eyes, IVD implantation was performed for the diagnosis of DME (n=65), BRVO (n= 32), CRVO (n= 10), non-infectious uveitis (n= 8), and RP (n=2). Because the IVD implant provides corticosteroid release for an average of 6 months, the second or third IVD implants were administered 5-6 months after the last dose if the macular edema persisted. Panretinal photocoagulation for a diagnosis of PDR was completed in all vitrectomized eyes. IVD was performed in 16 of these eyes due to DME and in 1 eye due to macular edema associated with BRVO. The distribution of diagnoses is shown in Table 1.

In non-vitrectomized eyes after the first IVD dose (n=117), IOP was 25 mmHg in 1 eye with DME at 1-3 days and in 1 eye with DME at 1 month. At 2 months after the first dose, IOP was in the 30-40 mmHg range in 1 eye with DME, 30 mmHg in 1 eye with BRVO, in the 25-30 mmHg range in 2 eyes with BRVO and DME, and 25 mmHg in a total of 5 eyes with DME (n=2), BRVO (n=2), and uveitis (n=1). One eye with DME had an IOP of 25 mmHg at 3 months, and 1 eye with DME had an IOP of 40 mmHg at 9 months. After the second dose (n=30), IOP was 30 mmHg in 1 eye with DME at 1-3 days, 30-40 mmHg in 2 eyes with DME and 25-30 mmHg in 1 eye with CRVO at 2 months, and 25 mmHg in 1 eye with BRVO at 3 months.

Among the vitrectomized eyes, none had IOP values of 25 mmHg or higher after the first dose of IVD (n=17), whereas IOP was 25 mmHg in 1 eye with DME at 1 month and 25-30 mmHg in 1 eye with DME at 2 months after the second dose of IVD (n=5). IOP higher than 25 mmHg was not observed after the third dose of IVD in any non-vitrectomized (n=10) or vitrectomized (n=1) eyes. The numbers of eyes with IOP values of 25 mmHg and higher according to group are shown in Table 2.

A total of 23 (17.2%) of the 134 eyes (21/117 non-vitrectomized, 2/17 vitrectomized) required IOP-lowering medication. Of these, 1 medication was initiated in 73.9%, 2 medications in 17.4%, and 3 medications in 8.7% of the eyes. IOP elevation that required surgical intervention was not observed in any of the eyes.

In non-vitrectomized eyes, the mean IOP was 14.01±2.36 mmHg before the first dose and 14.8±2.96 at 1-3 days, 16.71±3.97 at 1 month, 17.88±5.27 at 2 months, 15.54±3.35 at 3 months, 15.1±3.24 at 6 months, and 14.61±3.71 mmHg at 12 months after the first dose (Table 3). In non-vitrectomized eyes, the increases in mean IOP at 1-3 days, 1 month, 2 months, and 3 months were statistically significant compared to the mean IOP before the first IVD implant ($p<0.05$). Mean IOP at 6 months, 9 months, and 12 months did not differ significantly from mean IOP before the first dose ($p>0.05$). In non-vitrectomized eyes, there was no statistically significant change in mean IOP at 1-3 days, 1 month, 3 months, or 6 months after the second dose ($p>0.05$) but mean IOP at 2 months was significantly increased compared to before the second dose ($p<0.05$) (Table 4). In non-vitrectomized eyes, the increase in mean IOP from before to 1-3 days after the second dose was significantly greater than the increase in mean IOP at the same period after the first dose ($p<0.05$). However, the change in mean IOP at 1, 3, and 6 months compared to before implantation did not differ significantly between the first and second doses ($p>0.05$). Non-vitrectomized eyes showed no significant change in mean IOP at 1-3 days or 1, 2, 3, 6, and 9 months after the third dose ($p>0.05$).

Because the eyes were not homogeneously distributed in the vitrectomized and non-vitrectomized patient groups, as expected in real life conditions, and because the etiopathology and course of macular edema can vary, we also analyzed the eyes in our study in subgroups according to their diagnosis. In non-vitrectomized eyes treated with IVD due to DME (n=65), the mean IOP was 13.98±2.45 mmHg before the first dose and 15.00±3.12 at 1-3 days, 17.42±4.07 at 1 month, 18.08±5.41 at 2 months, 15.76±3.10 at 3 months, 15.14±3.41 at 6 months, 16.05±6.51 at 9 months, and 13.86±4.09 mmHg at 12 months. The increase in IOP was statistically significant at 1-3 days, 1 month, 2 months, and 3 months compared to the mean IOP before the first dose ($p<0.05$). Among these eyes that received a second IVD implant (n=13), the change in mean IOP was not significant at 1-3 days (16.31±4.70 mmHg), 1 month (15.80±3.90 mmHg), 2 months (29.00±9.64 mmHg), 3 months (19.63±2.72 mmHg), or 6 months (15.14±2.80 mmHg) compared to the mean IOP before the second dose (16.46±2.79 mmHg) ($p>0.05$). Of these eyes that received a third IVD implant (n=4), there was also no significant change in mean IOP at day 1-3 (14.50±1.73 mmHg), 1 month (16.67±3.22mmHg), or 3 months (13.00±1.41 mmHg) compared to the mean IOP before the third dose (15.75±2.63 mmHg) ($p>0.05$).

Table 1. Distribution of the diagnoses of patients who underwent intravitreal dexamethasone implantation

	Non-vitrectomized		Vitrectomized	
Diagnosis	**n**	**%**	**n**	**%**
DME	65	55.6	16	94.1
BRVO	32	27.4	1	5.9
CRVO	10	8.5	0	0
UVEITIS	8	6.8	0	0
RP	2	1.7	0	0
Total	117	100	17	100

DME: Diabetic macular edema, BRVO: Branch retinal vein obstruction, CRVO: Central retinal vein occlusion, RP: Retinitis pigmentosa

In the non-vitrectomized eyes treated with the IVD implant due to BRVO-related macular edema (n=32), the mean IOP was 14.22±2.17 mmHg before the first dose and 15.09±2.35 at 1-3 days, 15.83±3.99 at 1 month, 18.18±5.96 at 2 months, 14.79±2.96 at 3 months, 14.83±2.82 at 6 months, 14.71±3.90 at 9 months, and 14.75±2.75 mmHg at 12 months. Only the increase in IOP at 2 months was statistically significant compared to the mean IOP before the first dose ($p<0.05$). Among these eyes that received a second IVD implant (n=11), the changes in mean IOP at 1-3 days (14.55±2.66 mmHg), 1 month (18.29±3.15 mmHg), 2 months (19.67±5.86 mmHg), 3 months (19.40±3.58 mmHg), and 6 months (19.33±2.08 mmHg) were not statistically significant compared to the mean IOP before the second dose (14.91±2.39 mmHg) ($p>0.05$). In the non-vitrectomized eyes that received an IVD implant due to CRVO (n=10), the mean IOP was 14.10±2.60 mmHg before the first dose and 14.30±3.34 at 1-3 days, 16.00±4.03 at 1 month, 15.50±1.29 at 2 months, 16.89±4.78 at 3 months, and 19.00±2.83 mmHg at 12 months. There was no significant change in mean IOP at 1-3 days, 1 month, 2 months, 3 months, and 12 months compared to before the first dose or at 1-3 days, 1 month, 3 months, and 6 months compared to before the second dose ($p>0.05$).

In the non-vitrectomized eyes that received an IVD implant due to uveitis-related macular edema (n=8), the mean IOP was 13.25±2.55 mmHg before the first dose and 12.63±3.20 at 1-3 days, 14.75±2.50 at 1 month, 18.50±5.07 at 2 months, 13.33±3.79 at 3 months, and 15.00±2.00 mmHg at 12 months. The changes in mean IOP at 1-3 days, 1 month, 2 months, 3 months, and 12 months were not statistically significant compared to the mean IOP before the first dose ($p>0.05$). In the 2 non-vitrectomized eyes treated with IVD implant due to RP-related macular edema, the changes in mean IOP at 1-3 days (15.00±1.41 mmHg) and 1 month (16.00±0.00 mmHg) were not statistically significant compared to the mean IOP before the first dose (14.00 ±1.41 mmHg) ($p>0.05$). When compared according to diagnosis, no statistically significant difference was observed in terms of IOP changes at 1-3 days, 1 month, 2 months, 3 months, or 6 months compared to pre-implant IOP values with the first or second doses of IVD in non-vitrectomized eyes ($p>0.05$) (Table 5).

In the vitrectomized eyes treated with IVD due to DME (n=16), the mean IOP was 14.63±3.01 mmHg before the first dose and 13.56±2.83 at 1-3 days, 14.27±2.90 at 1 month, 15.71±3.50 at 2 months, 15.80±4.52 at 3 months, 18.29±3.20 at 6 months, 15.67±4.51 at 9 months, and 15.00±1.41 mmHg at 12 months. The changes in mean IOP at 1-3 days and at 1, 2, 3, 6, 9, and 12 months were not significant ($p>0.05$). Among these eyes that received a

second IVD implant (n=5), the changes in mean IOP at 1-3 days (17.20±3.35 mmHg), 1 month (19.00±4.97 mmHg), 2 months (20.00±6.00 mmHg), 3 months (20.67±2.3 mmHg), and 6 months (17.00±1.41 mmHg) were not statistically significant compared to the mean IOP before the second dose (15.60±4.34 mmHg) (p>0.05). Only one vitrectomized eye underwent IVD implantation for a diagnosis of BRVO. This eye received a single dose and showed no significant change in IOP at 1, 3, or 6 months (p>0.05).

Discussion

Corticosteroid-induced ocular hypertension is a complication seen in patients with a previous diagnosis of glaucoma or a family history of glaucoma. Elevated IOP values during corticosteroid therapy usually return to normal when treatment is interrupted. However, glaucomatous optic neuropathy may develop if the diagnosis is missed. Therefore, it is essential to closely monitor patients receiving corticosteroid therapy, especially children and patients with a family history of ocular hypertension or glaucoma. Studies have shown that IOP increases 1-2 months after intravitreal 4 mg triamcinolone injection and that this increase continues for approximately 3 months in non-vitrectomized eyes.[5,6] In a retrospective study evaluating 68 IVD implants in 38 eyes, 7 cases with IOP values above 21 mmHg were reported.[7] In the GENEVA study, IOP of 25 mmHg or higher was detected in 16% of patients treated with IVD, with the maximum increase on day 60 and return to pre-implantation levels on day 180.[8] These transient IOP increases did not require treatment or were controlled with short-term topical antiglaucomatous drops. Only 5 patients needed surgical intervention or laser trabeculoplasty. In another retrospective study evaluating 92 eyes, 50% of cases showed transient IOP elevation that did not require treatment, whereas 46.7% required glaucoma treatment and only 1 patient required glaucoma surgery.[9]

Chin et al.[10] reported in their study that IOP elevation was an important side effect of IVD implantation that was generally mild/moderate and transient. In a 3-year randomized controlled study examining patients who underwent 0.7 mg IVD implantation with DME as the indication, 144 (41.5%) of a total of 347 patients needed to start antiglaucomatous drops, 4 (1.2%) were treated with laser or surgical procedures, and only 1 case (0.3%) required incisional glaucoma surgery.[11] In our study, IOP elevation was controlled with topical antiglaucomatous drops in 23 (17.2%) of 134 eyes. None of these patients required glaucoma surgery. After the first dose of IVD, IOP peak values were observed at 2 months in the non-vitrectomized group and at 6 months in the vitrectomized group, while IOP values normalized in both groups after 6 months. After the second IVD dose, peak IOP was observed at 2 months in the non-vitrectomized group and at 3 months in the vitrectomized group, with IOP values again normalizing after 6 months in both groups. The findings in the non-vitrectomized group are consistent with the pharmacokinetics demonstrated in animal studies.[4] IOP elevation was also shown to peak at 2 months after IVD implantation in the GENEVA study[8] and in studies by Mazzarella et al.[9] and Meyer and Schönfeld.[12] In another retrospective study evaluating 59 eyes of 52 patients treated with IVD, it was reported that IOP elevation showed no cumulative effect in patients who received more than one implant.[10] In a 2015 study evaluating 15 eyes of 12 patients, there were 3 cases of IOP elevation controlled with topical treatment after the first, second, and third IVD doses.[13] In our study, there was no significant difference in IOP changes at 1, 3, and 6 months between the patients who received a single dose and those who

Table 2. Numbers of eyes in the vitrectomized and non-vitrectomized groups with IOP values of 25 mmHg or higher after receiving the first and second doses. In the non-vitrectomized group, IOP values of 25 mmHg or higher were recorded after the first dose in 13 eyes (8 with DME, 4 with BRVO, and 1 with uveitis) and after the second dose in 5 eyes (3 with DME, 1 with CRVO, and 1 with BRVO); in the vitrectomized group, IOP values of 25 mmHg or higher were recorded after the second dose in 2 eyes with DME

Non-vitrectomized (n=117)						**Vitrectomized (n=17)**	
IOP (mmHg)	**25**	**25-30**	**30**	**30-40**	**40**	**25**	**25-30**
First dose							
1-3 days	**1**	0	0	0	0	0	0
1 month	**1**	0	0	0	0	0	0
2 months	**5**	**2**	**1**	**1**	0	0	0
3 months	**1**	0	0	0	0	0	0
9 months	0	0	0	0	1	0	0
Second dose							
1-3 days	0	0	**1**	0	0	0	0
1 month	0	0	0	0	0	**1**	0
2 months	0	**1**	0	2	0	0	**1**
3 months	**1**	0	0	0	0	0	0

IOP: Intraocular pressure, DME: Diabetic macular edema, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion

received two doses. Eyes in our study that received multiple IVD implants showed a transient, mild to moderate increase in IOP with no statistically significant cumulative effect after the second and third doses. When compared by clinical diagnosis, there was no statistically significant difference in mean IOP values.

Pars plana vitrectomy (PPV) can be beneficial in the treatment of various conditions, such as diabetic retinopathy, retinal detachment, macular hole, epiretinal membrane, and intravitreal hemorrhage. IVD implantation is often necessary after PPV surgery. Viscosity decreases in vitrectomized eyes. It has been shown that intravitreal drugs such as anti-VEGF, triamcinolone, and amphotericin B are cleared from the vitreous faster in vitrectomized eyes.[15,16,17] A study conducted in monkey eyes demonstrated that the half-life of bevacizumab was reduced by 60% in vitrectomized eyes compared to non-vitrectomized eyes.[18] Niwa et al.[19] also showed that both intravitreal ranibizumab and aflibercept had shorter half-lives in vitrectomized eyes. These results suggest that the efficacy of intravitreal drug therapy may vary in non-vitrectomized and vitrectomized eyes. However, in a study conducted with rabbit eyes that received 0.7 mg IVD, a similar pharmacokinetic profile was observed in vitrectomized and non-vitrectomized eyes.[20]

The Ozurdex CHAMPLAIN study group published the results of a study evaluating the safety and efficacy of IVD for 26 weeks in 55 vitrectomized eyes of patients with DME in 2011. According to their report, 16% of the cases had elevated IOP. The proportion of patients with IOP values of 25 mmHg or higher was 9% at week 8 and decreased to 0% at week 26. In the same study, only 1 vitrectomized patient had IOP higher than 35 mmHg at week 8, while 17% of the cases required antiglaucomatous medication.[21] In their study evaluating the outcomes of IVD implant therapy in patients with DME, Çevik et al.[14] reported elevated IOP (25-30 mmHg) requiring medical treatment in 1 of 9 vitrectomized eyes and 2 of 31 non-vitrectomized eyes. In another study evaluating the results of IVD implantation in patients with DME, IOP values between

Table 3. IOP values (mmHg) after the first dose of intravitreal dexamethasone in non-vitrectomized and vitrectomized eyes

Surgery	IOP	n	Mean ± SD	Median	p
Non-vitrectomized	Preop	117	14.01±2.36	14	0.012*
	1-3 days	117	14.8±2.96	14	
	Preop	87	14.15±2.39	14	0.000*
	1 month	87	16.71±3.97	16	
	Preop	51	14.31±2.15	14	0.000*
	2 months	51	17.88±5.27	17	
	Preop	72	14.21±2.63	14	0.008*
	3 months	72	15.54±3.35	15	
	Preop	49	14.24±2.56	14	0.111
	6 months	49	15.1±3.24	15	
	Preop	30	14.33±2.43	14	0.973
	9 months	30	14.6±6.8	14	
	Preop	23	14.13±2.4	14	0.626
	12 months	23	14.61±3.71	14	
Vitrectomized	Preop	17	14.35±3.12	14	0.089
	1-3 days	17	13.41±2.81	14	
	Preop	12	13.75±3.11	14	0.680
	1 month	12	14±2.92	14	
	Preop	7	14.71±3.4	14	0.340
	2 months	7	15.71±3.5	16	
	Preop	11	14.36±3.75	14	0.441
	3 months	11	15.82±4.29	16	
	Preop	8	15.13±3.98	14	0.040*
	6 months	8	17.75±3.33	18	
	Preop	3	17±4.36	14	0.785
	9 months	3	15.67±4.51	16	
	Preop	2	18±5.66	14	0.655
	12 months	2	15±1.41	15	

Wilcoxon signed rank test, *p<0.05, IOP: Intraocular pressure, Preop: Before implantation, SD: Standard deviation

Table 4. IOP values (mmHg) after the second dose of intravitreal dexamethasone in vitrectomized and non-vitrectomized eyes

Surgery	IOP	n	Mean ± SD	Median	p
Non-vitrectomized	Preop	30	15.8±2.58	15	0.108
	1-3 days	30	14.8±3.84	14	
	Preop	16	15.81±1.91	15	0.378
	1 month	16	16.63±3.65	16.5	
	Preop	7	16.43±3.55	15	0.028*
	2 months	7	24.86±8.13	24	
	Preop	18	16.61±2.57	15	0.116
	3 months	18	18.39±3.74	17	
	Preop	12	16.08±2.91	15	0.664
	6 months	12	16.67±3.42	16	
Vitrectomized	Preop	5	15.6±4.34	14	0.593
	1-3 days	5	17.2±3.35	18	
	Preop	4	12.75±1.5	14	0.144
	1 month	4	19±4.97	19	
	Preop	3	15.33±5.77	15	0.109
	2 months	3	20±6	20	
	Preop	3	15.33±5.77	15	0.180
	3 months	3	20.67±2.31	22	
	Preop	2	17±7.07	17	1.000
	6 months	2	17±1.41	17	

Wilcoxon signed rank test, *p<0.05, IOP: Intraocular pressure, Preop: Before implantation, SD: Standard deviation

Table 5. Evaluation of changes in intraocular pressure measured before and after the first and second doses of intravitreal dexamethasone in non-vitrectomized eyes according to diagnosis

	CRVO	DME	UVEITIS	BRVO	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
First dose					
Preop - 1-3 days	0.2±2.97	1.02±3.24	-0.63±3.25	0.88±2.78	0.786
Preop - 1 month	2.13±4.79	3.30±4.33	-0.25±2.06	1.65±4.53	0.350
Preop - 2 months	0.00±2.71	3.88±5.57	4.25±2.22	3.88±6.01	0.564
Preop - 3 months	2.78±5.33	1.51±3.49	-1.00±1.00	0.68±3.45	0.452
Preop - 6 months	-	0.77±4.56	-	0.75±2.56	0.737
Second dose					
Preop - 1-3 days	-3.6±3.65	-0.15±3.34	-	-0.36±2.62	0.149
Preop - 1 month	-1.33±6.11	-0.40±2.70	-	2.86±3.93	0.311
Preop - 2 months	-	11.67±8.62	-	5.00±5.29	0.449
Preop - 3 months	-0.50±7.00	2.50±3.30	-	3.20±4.55	0.497
Preop - 6 months	1.05±9.19	-0.86±1.86	-	3.33±0.58	0.127

Kruskal-Wallis Test; CRVO: Central retinal vein occlusion, DME: Diabetic macular edema, BRVO: Retinal vein branch obstruction, IOP: Intraocular Pressure, Preop: Before implantation, SD: Standard deviation

21 and 35 mmHg were measured in both vitrectomized and non-vitrectomized eyes 1 to 3 months after administration and were controlled with topical treatment alone.[22] Özdemir et al.[23] also showed in their study that vitrectomized eyes receiving IVD for a diagnosis of DME had significant IOP elevation at 1, 3, and 6 months after implantation. In a retrospective study of 59 vitrectomized and 127 non-vitrectomized eyes, the frequency of IOP higher than 25 mmHg or at least 10 mmHg over baseline was 21.3% in non-vitrectomized eyes and 29.3% in non-vitrectomized eyes, IOP-lowering medication was required in 26.0% of non-vitrectomized eyes and 28.8% of vitrectomized eyes, and there was no significant difference between vitrectomized and non-vitrectomized eyes in terms of the incidence of ocular hypertension in patients with DME.[24] In the present study including 117 non-vitrectomized eyes, IOP after the first IVD dose was measured as 25 mmHg in 1 eye with DME at 1-3 days; 25 mmHg in 1 eye with DME at 1 month; 30-40 mmHg in 1 eye with DME, 30 mmHg in 1 eye with BRVO, 25-30 mmHg in 2 eyes with BRVO and DME, and 25 mmHg in a total of 5 eyes with DME (n=2), BRVO (n=2), and uveitis (n=1) at 2 months; 25 mmHg in 1 eye with DME at 3 months; and 40 mmHg in 1 eye with DME at 9 months. In the 30 non-vitrectomized eyes that received a second IVD dose, IOP was measured as 30 mmHg in 1 eye with DME at 1-3 days; 30-40 mmHg in 2 eyes with DME and 25-30 mmHg in 1 eye with CRVO at 2 months; and 25 mmHg in 1 eye with BRVO at 3 months. Among the 17 vitrectomized eyes in our study, we detected no significant IOP elevation after the first dose of IVD, while of the 5 vitrectomized eyes that received a second IVD dose, IOP was measured as 25 mmHg in 1 eye with DME at 1 month and 25-30 mmHg in 1 eye with DME at 2 months. We determined that the changes in IOP at 1-3 days, 1 month, 2 months, and 3 months after the first IVD dose were significant in non-vitrectomized eyes that underwent IVD implantation due to DME. In addition, we observed significant IOP elevation at 2 months in non-vitrectomized eyes that underwent IVD implantation due to BRVO-related macular edema. In the non-vitrectomized group, IOP measurements were found to be significantly higher at 1-3 days, 1 month, 2 months, and 3 months after IVD implantation, while there was no significant difference in vitrectomized eyes at these time points, which is inconsistent with the postoperative IOP elevation seen as a complication of vitrectomy surgery. We believe these results may be due to the fact that all of our vitrectomized patients had completed panretinal photocoagulation treatment for proliferative DRP and were not given silicone oil or gas, and had no intraoperative complications. This result may also be related to the more rapid vitreous clearance of IVD due to decreased viscosity in vitrectomized eyes, as demonstrated with other intravitreally administered drugs such as anti-VEGF, triamcinolone, and amphotericin B.[15,16,17]

In a study evaluating IVD implantation in vitrectomized patients with uveitis-related macular edema, the frequency of IOP elevation was 47.1%. IOP was measured as 22-30 mmHg and 30-40 mmHg in 7 eyes (41.1%) and 1 eye (5.9%), respectively, and returned to normal with medical treatment 8 weeks after implantation, with only 1 case required filtering surgery.[25] In addition, in a study examining 42 eyes undergoing IVD implantation for the indication of macular edema associated with non-infectious uveitis, IOP elevation over 21 mmHg was reported in 8 (36.4%) of 22 non-vitrectomized eyes and 12 (60%) of 20 non-vitrectomized eyes.[26] In the 8 non-vitrectomized eyes in our study that were treated with IVD for macular edema associated with non-infectious uveitis, IOP was measured as 25

mmHg in 1 eye at 2 months after the first dose and was below 25 mmHg in the other eyes. We detected no significant change in IOP levels at 1-3 days, 1 month, 2 months, 3 months, and 12 months after implantation.

Dexamethasone, fluocinolone acetonide, and triamcinolone were shown to activate different gene expression patterns in the human trabecular network.[27] The pharmacological activity of dexamethasone differs from that of triamcinolone. Dexamethasone is less lipophilic than triamcinolone and does not accumulate in the trabecular network to the same degree, and thus has a less pronounced IOP-elevating effect compared to triamcinolone.[28,29] When compared with the literature data, our findings support that IVD implants may be safer than intravitreal fluocinolone administration in terms of IOP elevation that may require glaucoma surgery.[30,31,32]

Conclusion

In this study we evaluated IOP changes in patients who underwent IVD implantation for the treatment of macular edema for various indications by grouping the eyes as those with and without a history of vitrectomy and also dividing them into subgroups according to their diagnosis. We observed that both vitrectomized and non-vitrectomized eyes that received the IVD implant generally had mild and transient IOP elevation that was independent of the indication for implantation and showed no cumulative effect in eyes that received second and third doses. This study has some limitations because it was conducted retrospectively and in a single center. The long-term prognosis of eyes with elevated IOP is unknown. These cases should be closely followed due to the risk of glaucoma in the future. A strength of our study is that we compared a large group of patients who received IVD implants for various indications by classifying them as vitrectomized and non-vitrectomized and dividing them into subgroups according to diagnosis. Studies with larger patient groups and more comprehensive follow-up may yield more definite results. Prospective clinical studies are needed to evaluate the safety of IVD implantation.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the ethics committee of the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., S.A.K., Concept: S.A.K., B.A., M.G., Design: B.A., M.G., S.A.K., Data Collection or Processing: M.G., A.Ç., Analysis or Interpretation: S.A.K., B.A., M.G., Literature Search: M.G., A.Ç., Writing: M.G., S.A.K.

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