Intraocular Pressure Changes after Single Dexamethasone Implant Injection: A real life clinical study, review of 1110 cases

Tek Deksametazon Implant Enjeksiyonu sonrası Göz İçi Basıncı Değişiklikleri: Gerçek hayat klinik çalışması, 1110 vaka serisi

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ABSTRACT

Purpose: To evaluate intraocular pressure (IOP) changes after single administration of dexamethasone implant (DI).

Methods: 1110 eyes of 1110 patients were included in this retrospective study. 726 eyes had DME, 262 eyes had macular edema secondary to branch retinal vein occlusion, and 122 eyes had macular edema secondary to central retinal vein occlusion. Data were collected at baseline, and each monthly visit. All adverse events during DI injection and during 6-month follow-up were recorded. IOP was measured at baseline and each visit.

Results: The mean ages was 61.6±8.5 year (range: 22-88 years). There was no significant differences in mean IOP measurements among values taken prior to injection and during each monthly visit afterward (p>.050). 168 eyes had IOP values of more than 20 mmHg during the follow-up period in general. 98 eyes did not receive any treatment, 65 eyes were treated with topical drops. 5 eyes were treated with selective laser trabeculoplasty. No surgery was required for any patient. No systemic adverse event observed.

Conclusion: DI injection may not carry a big risk of IOP rising in first 6 months. Also there may be no systemic adverse events associated with DI injection in first 6 months.

Key words: corticosteroids, dexamethasone implant, diabetic macular edema, intravitreal injection, retinal vein occlusion

ÖZ

Amaç: Tek bir Deksametazon Implant (DI) uygulaması sonrası göz içi basıncı (GİB) değişiklerini değerlendirmek.

Metot: 1110 hastanın 1110 gözü geriye dönük çalışmaya alındı. 726 gözde diyabetik maküla ödemi, 262 gözde retinal ven dal tıkanıklığına bağlı maküla ödemi ve 122 gözde santral retinal ven tıkanıklığına bağlı maküla ödemi vardı. Veriler başlangıçta ve her aylık visit sırasında toplandı. DI enjeksiyonu esnasında ve ilk 6 aylık takiplerdeki tüm yan etkiler kayıt edildi. GİB başlangıçta ve her vizitte kayıt edildi.

Bulgular: Ortalama yaş 61.6±8.5 (aralık: 22-88) idi. Enjeksiyon öncesi dönem ile aylık takiplerde ölçülen ortalama GİB değerleri arasında anlamlı fark yoktu (p>.050). Takiplerde 168 gözün GİB'ı 20 mmHg'yı aştı. 98 göz için ilave tedavi uygulanmadı, 65 göz için topikal damla tedavisi uygulandı. 5 göz selektif lazer trabeküloplasti ile tedavi edildi. Hiçbir hasta için cerrahi gerekmedi. Sistemik yan etkiye rastlanmadı.

Sonuç: DI enjeksiyonu ilk 6 aylık dönemde büyük bir GİB artış riski belki de taşımamaktadır. Ayrıca ilk 6 aylık dönem için belki de DI enjeksiyonuyla alakalı sistemik yan etki riski yoktur.

Anahtar kelimeler: kortikosteroid, deksametazon implant, diyabetik maküla ödemi, intravitreal enjeksiyon, retinal ven tıkanıklığı

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INTRODUCTION

As a common cause of sudden vision loss, macular edema secondary to either DR or RVO accommodates several treatment options.[1,2] Though laser photocoagulation was the mainstay of treatment for decades, intravitreal injections are now typically preferred, for which anti-vascular endothelial growth factors and corticosteroids are available as approved agents.[1,2]

Corticosteroids prevent leukocyte migration, stabilize the endothelial cell tight junctions, and inhibit the synthesis of vascular endothelial growth factor (VEGF), prostaglandins, and proinflammatory cytokines.[3] Given such effects, corticosteroids are commonly used in treating diabetic macular edema (DME) and macular edema secondary to RVO. They have also been used to treat ocular pathologies via oral, intravenous, and topical routes, as well as through both periocular and intravitreal injection.[3]

Yet, the systemic administration of corticosteroids may generate adverse ocular and systemic events, including glaucoma [4] cataract,[4] osteoporosis,[5] adrenal suppression,[6] and a cushingoid state,[6] while their topical or peribulbar administration may also induce similar event.[6,7] Since in most cases topical or peribulbar administration delivers suboptimal vitreous drug levels, recent direct intravitreal corticosteroid administration has conveniently bypassed the blood-ocular barrier and become a common method for treating an array retinal disorders.[8-10] In suit, alternative methods for extending the duration of the drugs' action and reducing its side effects have been a chief focus of recent research. Fluocinolone acetonide implants such as Retisert (Bausch & Lomb Inc., Rochester, NY, USA)[11] and Iluvien (Alimera SciencesInc., Alpharetta, GA, USA)[12] and the dexamethasone implant (DI) Ozurdex® (Actavis Allergan Inc., Parsippany, NJ, USA)[13] are examples of such new drug delivery systems.

It has been well known that corticosteroids can induce IOP raise likewise various drugs .[14] In this study, we aim to report IOP changes after single administration of DI.

METHODS

Study Design

The study sample included eyes of consecutive patients who received their first intravitreal DI injection as part of treatment for macular edema secondary to diabetes or retinal vein occlusions. Patients received their injections during May 2014-October 2015, and their medical records were reviewed retrospectively. The study was conducted according to the principles of the Declaration of Helsinki, and the approval of the Institutional Ethics Committee was obtained.

Examination and Eligibility Criteria

At baseline, participants received a standard ophthalmologic examination by experienced physicians that involved refraction, visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated fundoscopy. Optical coherence tomography and fundus fluorescein angiography were performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany). Inclusion criteria were first-time Ozurdex® implantation and a minimum 6-month follow-up period, while exclusion criteria were any history of glaucoma or ocular inflammation, ocular surgery within the previous 6 months, and missing any post-injection monthly visit. If both of a patient's eyes qualified for study, then the right eye was designated as the study eye for patients with an even birth month number and the left for those with an odd birth month number.

Dexamethasone Implant and Injection Technique

Ozurdex® is a biodegradable intravitreal implant that provides a sustained release of 0.7 mg preservative-free dexamethasone to the vitreous. The implant comprises a polylactic acid-glycolic acid matrix converted in vivo into carbon dioxide and water as well as eliminated by ocular tissue.[15] As the matrix dissolves, impregnated dexamethasone is released into the vitreous, sometimes as soon as a day after injection.[15,16]The US Food and Drug Administration (FDA) approved Ozurdex® for the treatment of macular edema following branch RVO (BRVO) or central RVO (CRVO) in 2009, of non-infectious ocular inflammation (i.e., uveitis) affecting the posterior eye in 2010, and of DME in 2014.

In this study, all injections were performed by experienced retinal specialistsin a clean room. Once each patient had provided informed written consent, intravitreal injection was administered under controlled aseptic conditions entailing sterile gloves, a sterile drape, and a sterile eyelid speculum. As recommended, adequate anesthesia and a broad-spectrum microbicide were applied to the periocular skin, eyelid (10% povidone–iodine), and ocular surface (5% povidone–iodine) prior to injection.

In this procedure, medical nurses first removed the foil pouch from the carton to assess any damage. The foil pouch was then opened over a sterile field and the applicator gently dropped on a sterile tray. Once the cap was removed from the applicator, the applicator was held in one hand while the other pulled the safety tab from the applicator. Ultimately, the nurses relayed the implant to the surgeon. The applicator's long axis was held parallel to the limbus and the sclera engaged at an oblique angle of about 45° with the bevel of the needle raised to create a shelved scleral path. The tip of the needle was advanced into the sclera parallel to the limbus and thereafter redirected toward the center of the eye and advanced until scleral penetration was complete and the vitreous cavity entered. The surgeon then depressed the actuator button until hearing an audible click, removed the needle in the same direction used to enter the vitreous, and applied light pressure with a cotton applicator to the injection site. An eye shield was used for at least 2 h after injection. Moxifloxacin hydrochloride ophthalmic solution 0.5%

(Vigamox®, Alcon Laboratories, Fort Worth, TX, USA) drops were thereafter used five times daily for 5 days.

Analysis:

Data were expressed as mean ± standard error of the mean. For intraocular pressure (IOP), normality was gauged with the Kolmogorov–Smirnov test. For before-and-after IOP comparison, paired samples t tests were performed. The Statistical Package for the Social Sciences version 22 (IBM, Chicago, IL, USA) was used for data analysis, and values of $p < .05$ were considered to be statistically significant.

RESULTS

Demographics

1110 eyes of 1110 patients were included in this retrospective study (Table 1).

Mean IOP was 15.3 ± 2.7 mmHg (range 10–19 mmHg) at baseline, yet changed to 17.4 ± 3.3 mmHg (range 12–34 mmHg) during month 1, 16.9 ± 3.2 mmHg (range 12–26 mmHg) during month 2, 16.7 ± 2.9 mmHg (range 12–22 mmHg) during month 3, 15.9 ± 2.5 mmHg (range 11–20 mmHg) during month 4, 15.6 ± 2.7 mmHg (range 12–19 mmHg) during month 5, and 15.5 ± 2.5 mmHg (range 12–20 mmHg) during month 6 (Figure 1). No differences emerged in mean IOP measurements among values taken prior to injection and during each monthly visit afterward (p=.244, p=.458, p=.520, p=.886, p=.986, p=.989).

Adverse Events and Their Treatments

Adverse events during the implant injection and during the first 6 months of follow-up were summarized in table (Table 2).

Table 1: *Baseline characteristics of the study population*

	Study population	DME	BRVO	CRVO
Number of eyes	1110	726 (%65.4)	262 (%23.6)	122 (%11.0)
Gender (female/male), n	475/635	352/374	112/150	55/67
Age				
Mean±SD	61.8±8.3	62.2±7.8	61.2±8.2	61.0±8.6
Min.-max.	22-88	44-88	22-84	30-88
Pseudophakic/Phakic, n	692/418	446/280	172/90	74/48
IOP, mmHg				
Mean±SD	15.5±2.7	15.9±2.4	16.0±2.4	15.8±2.9
Min.-max.	10-19	12-18	11-19	10-18

DME, diabetic macular edema; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; IOP, intraocular pressure

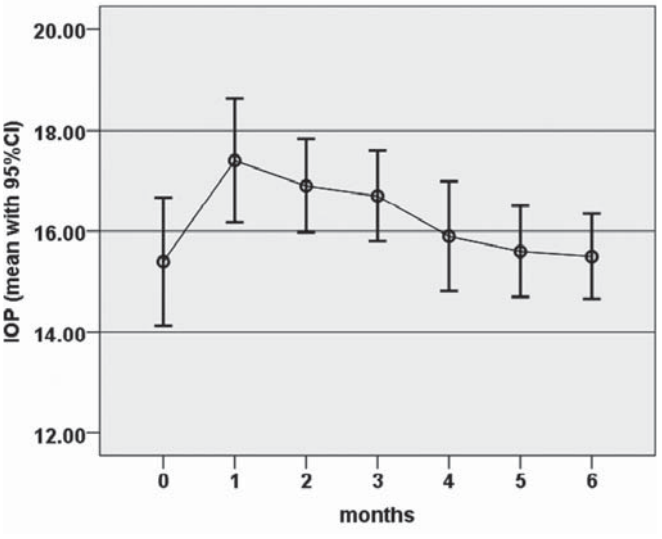

Figure 1 - *IOP Measurements at baseline and follow-ups.*

Table 2: *Adverse events during the injection and during the 6 months of follow-up*

Adverse events during the injection	**Eyes (n=1110)**	**Percentage**
Subconjunctival hemorrhage	48	4.32
Macroscopic reflux in injection area	398	35.86
Lens damage	1	0.09
Retinal tear	0	0
Adverse events during the 6 months follow-up	**Eyes (n=1110)**	**Percentage**
Increased intraocular pressure	173	15.59
Intravitreal hemorrhage	3	0.27
Transient epiteliopathy	35	3.15
Endophthalmitis	0	0
Retinal detachment	0	0
Systemic adverse events	0	0

A hundred and sixty eight eyes (%15.13) had IOP values of more than 20 mmHg during the follow-up period in general. These values ranged from 21–25 mmHg among 98 eyes (%8.83) who did not receive any treatment as a result and their IOP returned to normal by the end of the follow-up period. IOP values ranging from 26–30 mmHg in 65 eyes (%5.86) were controlled with topical drops. Five eyes (%0.45) had IOP values of more than 30 mmHg (32 mmHg and 34 mmHg) and underwent selective laser trabeculoplasty. No surgery was required for any patient.

In one patient, Ozurdex® was implanted into the crystalline lens accidentally (Figure 2). This patient with BRVO was 66 years old and had nuclear sclerosis in both eyes. One month following Ozurdex® injection, he developed cataract and IOP did not increase. Cataract surgery was performed conventional way, with additional posterior capsulorhexis and implant removal, and a three-piece intraocular lens was implanted into the capsular bag. No complications occurred during follow-ups.

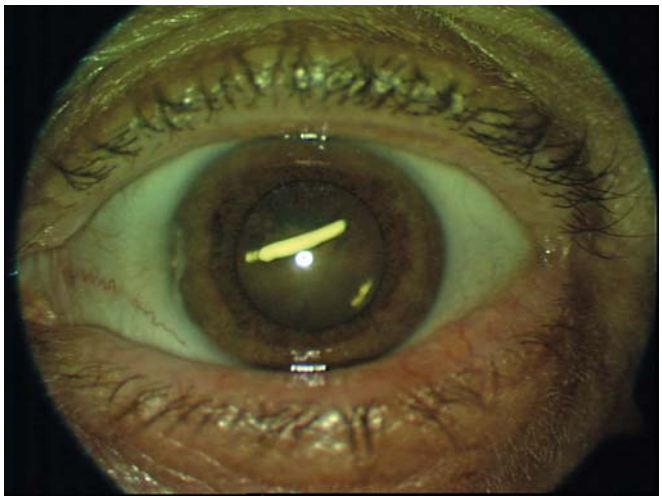

***Figure 2** - Accidental Ozurdex® implant injection into the crystalline lens.*

Three patients developed vitreous hemorrhage due to posterior vitreous detachment during the third month. In response, both patients were observed closely yet received no additional treatment, and their hemorrhages dissipated during the month 3.

DISCUSSION

In this study, subconjunctival hemorrhage, transient epitheliopathy, macroscopic reflux at the injection site, and crystalline lens damage were all adverse events observed during injection. Subconjunctival hemorrhage was resolved in a month's time without treatment. Transient epitheliopathy may be associated with the presence of povidone–iodine, yet in all cases disappeared without treatment.

Though no ocular hypotony or any kind of ocular infection emerged during the 6 months of follow-up, some patients had vitreous reflux at the injection site during the procedure, all of which disappeared in all cases without any treatment. Several patient-related factors may have contributed to such reflux, including baseline IOP, scleral thickness, and degree of vitreous liquefaction. By comparison, Rodrigues et al. reported 44.4% reflux rates after the intravitreal injection of bevacizumab and Höhn et al. 46.5%, while Ozkaya et al. reported 34.2% reflux rates after the intravitreal injection of ranibizumab.[17-19] Although DI implants were injected with a 22-gauge needle in this study; the reflux rate was 35.86%, which is similar to that observed in previous studies. All injections were performed in tunnel fashion, which could explain the similar reflux rates.

The patient in whom DI was implanted in the crystalline lens developed cataract and underwent successful cataract surgery, after which no vitreous reflux resulted, and the intraocular lens was implanted into the capsular bag. Among similar cases in the literature,[20,21] Berarducci et al. described a 78-year-old man who received an DI for the treatment of persistent cystoid macular edema and reported that the complication was successfully managed via the implant's surgical extraction from the lens body and the implant of a three-piece intraocular lens in the sulcus.[20] Furthermore, Coca–Robinot et al. reported two patients who received DI for the treatment of macular edema secondary to RVO.[20] After the accidental injections of the implant into the crystalline lens, both patients developed cataract involving increased IOP. Cataract surgery was performed along with an implant removal during months 3 and 6 for the cases, respectively. Ultimately, the authors concluded that surgery should be performed as soon as possible to prevent increased IOP.[20]

No eyes developed cataracts in this study, except the case who had accidental injection of DI to his crystalline lens, though this result should be interpreted in light of the relatively brief 6-month follow-up period, for a longer period might have resulted in cataracts requiring surgery, as occurred in a MEAD study of phase three clinical trials lasting 3 years.[22]

The rates of increased IOP levels of significant studies in the literature were presented in table (Table 3). In this study, 168 patients (%15.13) showed IOP values of more than 20 mmHg during the follow-up period in general. IOP was easily controlled in 163 of these cases with no treatment or topical drops, while laser treatment was used for five patients. By contrast, no patient needed trabeculectomy during the follow-up period. As such, the rate of IOP increase (15.13%) was at the lower end of the spectrum. While this study has presented single implant injection results, we speculate that multiple injections may induce increased IOP in more cases. For example, in a GENEVA multicenter study IOP increases of 10 mmHg or more from baseline were observed in 12.6% of patients after the first injection and in 15.4% after the second.[33] The same study also reported that IOP increases were usually transient and controlled with medication and/or ob-

Table 3: *IOP Changes after Ozurdex® implant injection in the literature (2013-2015)*

Author	Study type	Follow-up time	Year of publishing	Participants (eyes)	IOP increase	Treatments of IOP increase
MEAD Study[a]	Prospective, phase III clinical trials	3 years	2014	347*	over 25 mmHg at any visit 111 cases (32%), over 35 mmHg at any visit 23 cases (6.6%), increase of 10 or more mmHg from baseline 96 cases (27.7%)	2 cases (0.6%) required trabeculectomy, others controlled with no therapy, medication or laser.
Maggio et al.[b]	Retrospective	1 year	2014	43	12 cases (27.9%) had transient IOP increase	5 controlled with topical drops and others with no therapy.
Escobar-Barranco et al.[c]	Prospective	6 months	2015	76	6 cases (7.9%) had transient IOP increase	All cases controlled with bimatoprost drops.
OMAR Study[d]	Retrospective	1 year	2015	35	11 cases (31%) had transient IOP increase	All cases controlled with topical drops.
Bellocq et al.[e]	Retrospective	6 months	2015	50	10 cases (20%) had transient IOP increase	7 cases controlled with one single drop, and 3 cases controlled with two drops.
Khurana et al.[f]	Retrospective	1 year	2015	18	2 cases (11%) had transients IOP increase	All cases controlled with topical drops.
Reid et al.[g]	Retrospective	6 months	2015	61	10 cases (12%) had IOP over 25 mmHg	9 cases (11%) controlled with topical drops and 1 case (1.2%) need deep sclerectomy
Mayer et al.[h]	Prospective	1 year	2013	64	40% of cases had IOP increase over than 5 mmHg	All cases controlled with topical drops except one case controlled with laser.
Capone et al.[i]	Retrospective	6 months	2014	289	97 cases (33.7%) has IOP over 25 mmHg	29.1% cases controlled with topical drops and 1.7% of patients required surgery.
Zamil[j]	Retrospective	6 months	2015	11	No cases had IOP increase	
Zalewski et al.[k]	Retrospective	5 months	2014	6	No cases had IOP increase	
Mathew et al.[m]	Prospective	9 months	2014	30	2 cases (6.7%) had IOP increase	All cases controlled with topical drops.

*347 cases had 0.7 mg Dex implant; a, reference 22; b, reference 23; c, reference 24; d, reference 25; e, reference 26; f, reference 10; g, reference 27; h, reference 28; i, reference 29; j, reference 30; k, reference 31; m, reference 32

servation.[33] Changes in IOP in the DI implanted eyes peaked at day 60 in that study,[32] at day 30 in Bellocq et al.'s study,[26] and at day 30 in the present study.

Ozkok et al. compared Ozurdex® implants and triamcinolone acetonide injection for refractory cystoid macular edema in RVO and reported no differences between the implant and triamcinolone regarding the incidence of side effects.[25] IOP increase of more than 6 mmHg occurred at a rate of 20% in the implant group and of 25.6% in the triamcinolone group, though this difference was not statistically significant.[25] Conversely, Kiddee et al. showed that DI implants had a lower rate of IOP increase than triamcinolone and fluocinolone implants.[34] In their study, the IOP increase rate was 32% following triamcinolone implant, 66% and 79% following 0.59 and 2.1 mg fluocinolone implants, respectively, and 15% following DI.[32]

In this study no unexpected adverse events occurred, and implants demonstrated excellent systemic safety.

This study has several limitations, including its retrospective nature, brief follow-up period, the presentation of adverse events from a single injection, and no presentation of anatomical and functional results. At the same time, this real life clinical study consisted of the most cases among single-center studies, which proved to be a strong side of the study.

In conclusion, Ozurdex® was found not to be at high risk in terms of increased IOP in first 6 months from the injection. Further studies should confirm the above data and compare treatment options for any adverse events subsequent to injections.

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