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ORIGINAL ARTICLE

Effect of intravitreal dexamethasone implant (Ozurdex®) injections on corneal biomechanical properties measured using ocular response analyzer

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Abstract

Purpose: The purpose of the study was to evaluate Ocular Response Analyzer (ORA) measurements and endothelial cell density (ECD) in patients who received intravitreal dexamethasone implant (Ozurdex®) injection for diabetic macular edema.

Methods: Twenty-three eyes of 13 patients who receive intravitreal dexamethasone implant injection (Group 1) for diabetic macular edema and 33 eyes of 33 healthy individuals (Group 2) were included in the study. All participants underwent a complete ophthalmologic examination including intraocular pressure measurement with Goldmann applanation tonometer (IOP-GAT), ORA measurements, and specular microscopy.

Results: The mean age of the patients was 65.43 ± 8.20 (49–75) in Group 1 and 61.94 ± 4.52 (56–71) in Group 2 ($p=0.114$). The mean IOP-GAT was significantly higher in Group 1 (18.22 ± 3.41 ; range 12–28 mmHg) than in Group 2 (15.41 ± 3.07 ; range 8–21 mmHg) ($p=0.02$). The mean ECD was 2632.4 ± 209.6 (2232–3067) cell/mm² in Group 1 and 2567 ± 206.37 (2140–2854) cell/mm² in Group 2 ($p=0.60$). The mean corneal resistance factor (CRF) was 12.16 ± 2.35 (7.4–15.3) mmHg in Group 1 and 10.18 ± 1.83 (6.7–14.2) mmHg in Group 2 ($p=0.02$). Mean corneal hysteresis (CH) in Groups 1 and 2 was 8.87 ± 2.45 (4.1–13.4) mmHg and 10.47 ± 1.43 (6.9–13.2) mmHg, respectively ($p=0.001$). Mean corneal compensated IOP and Goldman correlated IOP (IOPg) were higher in Group 1 (24.72 ± 7.12 ; range 12.1–36.4 mmHg and 23.21 ± 7.01 ; range 14.2–36.2 mmHg) than in Group 2 (14.95 ± 3.6 ; range 8.3–22.9 mmHg and 14.33 ± 3.84 ; range 6.3–21.7 mmHg) ($p<0.001$). IOP-GAT was correlated with IOPg ($p=0.01$).

Conclusion: Intravitreal Ozurdex® injection effects IOP, while it has no significant effect on ECD. Ozurdex® injections changed corneal biomechanical properties such as CH and CRF. Thus, ORA may be a useful to avoid underestimating the IOP and missing the alteration of elastic properties of the cornea.

Keywords: Diabetic macular edema; intravitreal dexamethasone implant; ocular response analyzer.

Intravitreal corticosteroid agents have been used for many years in the treatment of various diseases involving the macula due to their strong anti-inflammatory effects. ^[1] Intravitreal dexamethasone implant (Ozurdex®, Allergan,



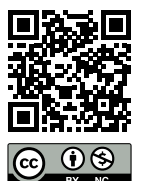
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Irvine, CA, USA) as a slow-release synthetic corticosteroid is indicated in macular edema due to retinal vein occlusion, non-infectious posterior uveitis and diabetic retinopathy. It is injected intravitreally by using a 22-gauge transconjunctival needle through a small scleral puncture. The implant contains 0.7 mg of biodegradable corticosteroid, the effect of which can last up to 6 months.^[2,3]

Ozurdex[®] implant, which is widely used due to its strong effectiveness, has some undesirable side effects. The most known and expected adverse effects are intraocular pressure (IOP) elevation and cataract formation. However, its effects on corneal endothelium and biomechanical properties have not been clearly defined.^[4]

Ocular response analyzer (ORA) is a non-contact tonometer, which evaluates the corneal response to a 25 millisecond air pulse pressure and allows bi-directional applanation measurement. It measures corneal biomechanical properties including corneal compensated IOP (IOPcc), Goldman correlated IOP (IOPg), corneal hysteresis (CH), and corneal resistance factor (CRF). IOPcc is a IOP measurement which is independent from corneal properties, and IOPg is defined as average of the inward and outward applanation pressures which is related to IOPGoldman. CH shows viscoelastic nature of the cornea and CRF is the measurement of the corneal resistance to applanation force.^[5,6] On the other hand, specular microscopy is a non-invasive imaging tool that gives data about corneal endothelial density and morphology.^[7]

The aim of this study was to evaluate the effects of dexamethasone implant on corneal biomechanical properties as measured by ORA and endothelial cell density (ECD) measured by specular microscopy in patients who received intravitreal dexamethasone implant (Ozurdex[®]) injection for diabetic macular edema.

Materials and Methods

This prospective and cross-sectional study was carried out in accordance with the principles of the Declaration of Helsinki, at Ege University Faculty of Medicine, Department of Ophthalmology. This study was approved by the Ethics Committee of Ege University and written informed consent was obtained from all participants.

Patients who received intravitreal dexamethasone implant injections with the diagnosis of macular edema due to diabetic retinopathy were included in the study (Group 1). Age and gender matched healthy individuals were assigned as the control group (Group 2).

Medical data of the patients including age, gender, and number of injections were reviewed. All participants un-

derwent a complete ophthalmologic examination including best corrected visual acuity, IOP measurement with Goldmann applanation tonometer (IOP-GAT), slit-lamp examination, and fundus examination. Topical anti-glaucomatous therapy was initiated in eyes with an IOP-GAT value above 25 mmHg.

In addition, corneal biomechanical parameters such as CH, CRF, IOPg, and IOPcc were measured by the ORA (ORA, Reichert Ophthalmic Instruments, Depew, NY, USA) in all subjects. Central corneal thickness (CCT) and corneal ECD were measured by specular microscopy (Nidek Co, Ltd, Gamagori, Japan). All measurements were performed by a single researcher 1 month after the last injection. To avoid daily fluctuations in the parameters, all measurements were performed during the same period (afternoon) of the day.

Patients with a history of previous ocular surgery (including corneal refractive surgery and phacoemulsification) or trauma, receiving intravitreal anti-VEGF therapy, using topical or systemic steroids, previously diagnosed with glaucoma, and using anti-glaucomatous drops were excluded from the study.

Statistical Analysis

Statistical analysis was performed using SPSS v.20.0 (IBM Co. Armonk, NY, USA). The normality of parameters was evaluated with Shapiro–Wilk test. The data which distributed normally compared with student t test, and the data which not distributed normally compared with Mann–Whitney U test. A value of <0.05 was accepted as statistically significant.

Results

Twenty-three eyes of 13 patients (Group 1) who received intravitreal dexamethasone implants with the diagnosis of diabetic macular edema, and 33 eyes of 33 age- and gender-matched healthy participants (Group 2) were included in the study. The mean number of Ozurdex[®] injection was 2.76 ± 1.2 (1–5) in Group 1.

The mean age of the patients was 65.43 ± 8.20 (49–75) in Group 1 and 61.94 ± 4.52 (56–71) in Group 2. The difference was not statistically significant ($p=0.114$). Male/Female ratio was 15/8 in Group 1 and 20/13 in Group 2.

The mean IOP-GAT was significantly higher in Group 1 (18.22 ± 3.41 ; range 12–28 mmHg) than in Group 2 (15.41 ± 3.07 ; range 8–21 mmHg ($p=0.02$)). Topical anti-glaucomatous therapy was required in 8 (34.7%) of 23 eyes, and all of these eyes received more than 3 Ozurdex[®] implant injections.

Table 1. Effects of clinical and demographical properties of MS patients on measures of CC

	Parameters (Mean±SD [range])	Study group (Group 1)	Control group (Group 2)	p value*
ORA measurements	CH	8.87±2.45 (4.1–13.4)	10.47±1.43 (6.9–13.2)	=0.001
	CRF	12.16±2.35 (7.4–15.3)	10.18±1.83 (6.7–14.2)	=0.02
	IOPcc	24.72±7.12 (12.1–36.4)	14.95±3.6 (8.3–22.9)	<0.001
	IOPg	23.21±7.01 (14.2–36.2)	14.33±3.84 (6.3–21.7)	<0.001
GAT	IOPGoldman	18.22±3.41 (12–28)	15.41±3.07 (8–21)	=0.02

*P<0.05 was considered statistically significant. ORA: Ocular Response Analyzer; GAT: Goldmann applanation tonometer; CH: Corneal hysteresis; CRF: Corneal resistance factor; IOPcc: Corneal compensated intraocular pressure; IOPg: Goldman correlated intraocular pressure; IOPGoldman: Intraocular pressure measurement with Goldmann applanation tonometer; SD: Standard deviation.

The mean CCT was 534.82±32.10 (470–602) µm in Group 1 and 545±28.35 (487–613) µm in Group 2, there was no statistically significant difference (p>0.05). The mean corneal ECD was 2632.4±209.6 (2232–3067) cell/mm² in Group 1 and 2567±206.37 (2140–2854) cell/mm² in Group 2, the difference was not statistically significant (p=0.60). There was a statistically significant difference between the groups in terms of all corneal biomechanical parameters (CH, CRF, IOPcc, and IOPg) measured with ORA (Table 1).

Correlation analysis was performed between corneal biomechanical properties, number of Ozurdex® injections and IOP-GAT values. Although there was a relatively high correlation between the number of Ozurdex® injection and CRF, it was not statistically significant (p=0.07). There was no statistically significant correlation between Ozurdex® implantation number and CH, IOPg, and IOPcc (p>0.05). IOP-GAT showed a significant correlation with IOPg (p=0.01) as expected.

Discussion

In the current study, IOP measurement with GAT, CCT and ECD measurement with specular microscopy, and corneal biomechanical properties with ORA were evaluated in patients who received Ozurdex® intravitreal implant injection. According to the results of this study, intravitreal Ozurdex® injections significantly affected IOP and corneal biomechanical properties such as CH and CRF, while it had no significant effect on ECD.

Ozurdex is a slow-release dexamethasone implant that can be easily injected into the vitreous cavity through a small scleral puncture. It is indicated and widely used in various retinal diseases that result with macular edema. However, intravitreal Ozurdex implant has undesirable side effects and these may limit its use in certain cases. Ocular hypertension and cataract are well-known and relatively common adverse effects of the Ozurdex® implant.^[1–4] The SAFODEX study reported a 28.5% incidence of ocular hy-

pertension following Ozurdex® implant injection.^[8] In the present study, IOP-GAT was significantly higher in patients who received Ozurdex® implant injection than in the control group. Consistent with the literature, 34.7% of the eyes required topical antiglaucomatous treatment following Ozurdex® implant injection.

Early diagnosis and timely treatment are vital to prevent permanent optic nerve damage and blindness in glaucoma. Therefore, accurate measurement of IOP is crucial.^[9] Although GAT is still the gold standard method for IOP measurement, different IOP measurement methods have been defined. ORA is a device that can measure IOP taking into account corneal biomechanics. It is known that changes in corneal biomechanical properties may affect IOP measurements.^[5,6,10] In the current study, GAT-measured IOP and ORA-measured IOPs were different in the Ozurdex® implant group, while they were similar in the control group. The mean IOP-GAT was lower than the mean IOPcc and IOPg in the Ozurdex® implant group. These findings suggest that, there may be some changes in corneal biomechanics after Ozurdex® implantation, resulting in an underestimation of IOP.

Apart from the IOP itself, many different factors have been proposed to be associated with the development and progression of glaucoma.^[9] The relationship between corneal biomechanical parameters, especially CH, and glaucoma has been investigated recently. CH defines the viscoelastic damping of the cornea to response a 25 millisecond air pulse pressure. Low CH was proposed as an independent risk factor for glaucoma progression.^[11] De Moraes et al.^[12] stated that the lower CH was correlated with faster glaucoma progression. Yulek et al.^[13] reported the lower CH in patients with steroid-induced ocular hypertension. The current study demonstrated lower CH in the Ozurdex® implant group compared with the controls, while CRF was significantly higher in the Ozurdex® implant group.

It is well known that corneal disorders such as keratoconus and keratitis, and refractive surgery change the biomechanical properties of the cornea. However, other possible influencing factors cannot be defined clearly.^[14] Intravitreal injection of Ozurdex[®] implant causes some structural changes in the eye due to the its long-acting steroid release. As well as the direct effect of the steroid on trabecular meshwork, the implantation procedure itself can cause some changes in corneal biomechanics. Intravitreal implantation of Ozurdex[®] through a scleral entry 3.5–4 mm from the limbus may trigger changes in corneal biomechanical properties including CH.^[4,15] This finding is supported by the study of Seymenoglu et al.,^[16] who found significantly lower CH 1 month after 23 Gauge pars plana vitrectomy.

Corneal decompensation may occur as a complication of intravitreal Ozurdex[®] that is inadvertently injected into the anterior chamber. However, the exact mechanism of decompensation is not well-defined. It might be caused by direct mechanical trauma of the 6 mm long and 0.45 mm diameter implant to the endothelium. It may also occur due to drug toxicity triggered by dexamethasone or other components of the implant.^[15,17] The previous studies have established specific receptors in the corneal endothelium that regulate glucocorticoid activity.^[18] This suggests that the prolonged release of corticosteroid by Ozurdex[®] may also have a potentially toxic effect on the corneal epithelium. However, Guler et al.^[15] did not report permanent reduction in ECD after intravitreal Ozurdex[®] injections. Similarly, in the current study, there was no significant difference in ECD between the two groups. This can be interpreted as Ozurdex[®] implant injection does not affect the ECD unless it is injected into the anterior chamber. Yet, further studies are needed to draw conclusions, particularly on the long-term effect.

The main limitations of this study are small sample size and its cross-sectional nature. ORA and specular microscopy measurements were performed only after injections and there is no data regarding the pre-injection time. Prospective, long-term studies with larger patient populations are required to evaluate the potential impact of the implant and the implantation procedure on corneal biomechanics.

Conclusion

Uncomplicated multiple Ozurdex[®] injections do not affect ECD. However, these injections seem to change the IOP and corneal biomechanical properties. It is still unclear whether the latter effect is due to increased IOP or scleral entry, and further investigations should be considered to clarify this dilemma.

Ethics Committee Approval: This study was approved by Ege University Faculty of Medicine Ethics Committee (date: 20.02.2019; number: 19-2.1T/42).

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