The effects of repeated Ozurdex injections on ocular hypertension

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Purpose: The purpose of this study was to correlate the degree of ocular hypertension with the number of Ozurdex injections.

Methods: Intraocular pressure (IOP) fluctuations for a total of 183 injections were studied over a period of at least 12 months. The main indications for treatment were uveitis, diabetic macular edema, and retinal vein occlusion.

Results: Results of the study demonstrate that repeated Ozurdex injections do not increase the frequency of IOP spikes beyond 30 mmHg. For lower IOPs, however, a positive correlation exists. Furthermore, patients with primary open angle glaucoma and uveitis had the highest IOP response to repeated injections. On average, patients with an IOP of \(\geq 28.6\) mmHg received pressure lowering medications, after which their IOP reached a stable level (16.7 mmHg) without the need for additional interventions.

Conclusion: The data support the conclusion that multiple Ozurdex injections does not increase the frequency of IOP spikes beyond 30 mmHg, but patients still must be closely monitored if they have a history of primary open angle glaucoma.

Keywords: Ozurdex, dexamethasone, glaucoma, intraocular pressure, ocular hypertension

Introduction

Dexamethasone intravitreal implant (0.7 or 0.35 mg) (Ozurdex, Allergan, Inc., Irvine, CA, USA), also known as Ozurdex\(^4\), consists of micronized dexamethasone in a biodegradable copolymer of polylactic-co-glycolic acid which slowly releases steroids into the vitreous over a period of about 6 months.\(^1,2\) Multiple studies show that dexamethasone intravitreal implant is an effective means of improving best corrected visual acuity (BCVA) and reducing diabetic macular edema (DME) in patients that are resistant to anti-VEGF (vascular endothelial growth factor) therapy.\(^3\) Likewise, the dexamethasone implant is an effective adjunct treatment for management of macular edema in patients with chronic non-infectious uveitis or retinal vein occlusions.\(^4,6\)

Elevated intraocular pressure (IOP) is a major downside to dexamethasone implants and, yet, it is not clear how repeated injections affect the incidence of ocular hypertension. A number of studies, including the MEAD (macular edema: assessment of implantable dexamethasone in diabetes) study, have investigated the effects of Ozurdex injections on intraocular pressure. According to the MEAD study, IOPs were usually controlled with medication or no therapy, while 0.6% of patients in the 0.7 mg dexamethasone implant group and 0.3% in the 0.35 mg implant group required trabeculectomy.\(^7\) A recent study also demonstrated that ocular hypertension, which is defined as intraocular pressure of at least 25 mmHg or an increase of at least 10 mmHg from baseline, was recorded for 28.5% of injected eyes, and that IOP lowering medication was required for 31% of...
eyes. The study concluded that episodes of Ozurdex-mediated ocular hypertension are generally transient and can be successfully managed with topical treatment.\textsuperscript{8}

It is now clear that ocular hypertension caused by Ozurdex injections can be managed with topical medications. However, it is not yet clear how repeated injections of Ozurdex affect the successful control of IOP with topical medications. The purpose of this study is to investigate the frequency and degree of ocular hypertension associated with sequential injections of dexamethasone intravitreal implants, and to determine whether topical medications are sufficient for controlling IOP in these patients.

\section*{Methods}

This retrospective review was approved by Specialty Surgery Center IRB prior to the start of the study. The study was conducted on patients who received one or more dexamethasone implants, and all patients signed a consent form allowing their protected health information to be used. The primary outcome included highest mean IOP and frequency/degree of ocular hypertension that developed following treatments. The degree of ocular hypertension was defined as IOP measurements of $\geq23$ (mild), $\geq25$ (moderate), or $\geq30$ (severe) mmHg. These values were selected based on a review of other literatures as well as the definition of ocular hypertension by our glaucoma specialists ($\geq23$ mmHg). The main indications for treatment were uveitis, diabetic macular edema (DME), and branch (BRVO) or central (CRVO) retinal vein occlusion. Statistical significance was determined using one-way analysis of variance (ANOVA). Topical medications that were used for lowering intraocular pressure include combinig, brimonidine, cosopt, simbrinza, bimatoprost, travoprost, latanoprost, timolol, and dorzolamide. To avoid selection bias, patients who showed IOP spikes were not switched to Anti-VEGF, and repeated Ozurdex injections were not withheld.

\section*{Results}

A total of 183 eyes were treated for 171 patients, where 139 eyes received a single injection, 25 eyes received two injections, and 19 eyes received three injections. As Figure 1 depicts, the frequency of ocular hypertension was: mild (31%, 26%, 53%), moderate (26%, 24%, 42%), and severe (12%, 12%, 11%) for single, two, or three injections, respectively. On average, patients had the highest IOP after single injection followed by CRVO (21.8±1.1), BRVO (21.1±1.1), and DME (20.7±1.1) groups (uveitis versus DME P-value=0.054) (Figure 3). The values in bracket represent IOP changes in mmHg (mean ± SEM).

\begin{figure}
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\includegraphics[width=\textwidth]{figure1}
\caption{The frequency and degree of IOP spike following one, two, or three injections of Ozurdex. The frequency of ocular hypertension for single, two, or three injections was as follows: mild (31%, 26%, 53%), moderate (26%, 24%, 42%), and severe (12%, 12%, 11%). The values in brackets represent IOP changes in mmHg (mean ± SEM).}
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\begin{figure}
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\includegraphics[width=\textwidth]{figure2}
\caption{Patients with POAG had a significantly higher IOP compared to patients with no medical or family history of glaucoma (20.8±0.65) (P-value=0.004) (Figure 2). Among the treatment groups, patients with uveitis (24.3±1.7) had the highest IOP after single injection followed by CRVO (21.8±1.4), BRVO (21.1±1.1), and DME (20.7±1.1) groups (uveitis versus DME P-value=0.054) (Figure 3). The values in bracket represent IOP changes in mmHg (mean ± SEM).}
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\includegraphics[width=\textwidth]{figure4}
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The frequency and degree of ocular hypertension associated with sequential injections of dexamethasone intravitreal implants, and to determine whether topical medications are sufficient for controlling IOP in these patients.

\section*{Discussion}

Cataract and ocular hypertension are the main long-term side effects of Ozurdex, but the degree of ocular hypertension is
Among patients who have received an Ozurdex implant, patients with a prior history of POAG, and even possibly patients with a positive family history of glaucoma. Therefore, Ozurdex implants should be used with caution in patients with a prior history of POAG, and possibly a combination of both mechanisms. However, the benefits of Ozurdex injection for uveitis treatment will likely outweigh the potential temporary IOP spike seen in these patients.

Figure 3 Patients with uveitis had the highest mean IOP spike after a single injection followed by CRVO, BRVO, and DME groups. The IOP measurements for different treatment groups were as follows: uveitis (24.3±1.7), CRVO (21.8±1.4), BRVO (21.1±1.1), and DME (20.7±1.1) groups. The values in brackets represent IOP changes in mmHg (mean ± SEM).

Abbreviations: IOP, intraocular pressure; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; DME, diabetic macular edema; SEM, standard error of the mean.

Results of this study show that sequential dexamethasone implant injections increase the incidence of mild (≥23 mmHg) and moderate (≥25 mmHg) IOP elevation, but not severe (≥30 mmHg) hypertension. Among treatment groups, patients with primary open angle glaucoma (POAG) had a significantly higher IOP spike compared to the control group. Therefore, given their increased susceptibility for IOP elevations, dexamethasone implants should be used with caution in patients with POAG. Finally, patients with uveitis had the highest IOP spike, presumably due to the uveitis-mediated IOP spike, as well as previous treatments with steroids.

Conclusion
Results of this study show that sequential dexamethasone implant injections increase the incidence of mild (≥23 mmHg) and moderate (≥25 mmHg) ocular hypertension, but not severe (≥30 mmHg) hypertension. Among treatment groups, patients with primary open angle glaucoma (POAG) had a significantly higher IOP spike compared to the control group. Therefore, given their increased susceptibility for IOP elevations, dexamethasone implants should be used with caution in patients with POAG. Finally, patients with uveitis had the highest IOP spike, presumably due to the uveitis-mediated IOP spike, as well as previous treatments with steroids.

Disclosure
Dr Michael A Singer’s disclosures are as follows: Consultant for Allergan, Genentech, Regeneron, Santen, Clearside, Aerpio, Alimera. Research support from Allergan, Genentech, Regeneron, Ampio, Optos, Aerpio, Allegro, Diachii, Clearside. None of the other authors have relevant conflicts of interest.

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