Ocular hypertension management in long-term treatments with intravitreal dexamethasone implants: a 3-year experience

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Abstract

Purpose. A commonly recognized complication of intravitreal steroids is ocular hypertension (OHT). The aim of this study was to investigate the effectiveness of pharmacotherapy in controlling this side effect, even in patients receiving sequential injections.

Methods. A total of 146 injections were performed on 78 patients over 3 years. 78 eyes were treated with 1 injection, 44 eyes were treated with 2 injections; 24 eyes were treated with 3 injections. The intravitreal corticosteroid used in this observational study is 0.7mg dexamethasone, commercially known as 0.7mg Ozurdex®.

Results. Following the first injection, mean intraocular pressure (IOP) increased by 1.90 mmHg. Following the second injection, mean IOP increased by 0.23 mmHg. Following the third injection, there was no statistically significant change. Patients with IOP >= 21mmHg (7% of all participants) were started on topical pressure-lowering medications.

Conclusion. Intravitreal dexamethasone implants increased IOP of variable degrees in different patients. However, secondary OHT was effectively controlled with pharmacotherapy alone. This allowed for continuation of dexamethasone therapy.

Key words: Ozurdex®, dexamethasone, glaucoma, intraocular pressure, ocular hypertension

Introduction

Corticosteroids can cause ocular hypertension (OHT) (1-3), regardless of their route of administration (systemic, topical, periocular or intravitreal). The use of intravitreal corticosteroids for the treatment of posterior segment disease has increased significantly over the last decade (4,12). Recognized complications include secondary ocular hypertension, cataract formation and dislocation of the implant into the anterior chamber (5). Ocular hypertension might occur immediately after the injection due to increased intravitreal volume, or weeks to months later because of increased outflow resistance through the trabecular meshwork (13,16).

In recent years, intravitreal dexamethasone injections (Ozurdex 0.7mg by Allergan Inc, Irvine, CA) have gained popularity over intravitreal anti-VEGF injections for the treatment of macular edema (ME) secondary to retinal vein occlusion (RVO) (17-28), diabetes (DME) (3-5,14,17-19,23,29,31), surgery and uveitis (9,23).

Side effects of intravitreal dexamethasone are similar to those of other corticosteroids, such as triamcinolone acetonide and fluocinolone acetonide, but ocular hypertension is generally milder and better tolerated (1-3).

In fact, ocular pressure elevations are generally transient and successfully controlled with pharmacotherapy alone (1-3). Numerous studies have investigated the efficacy and tolerability of Ozurdex implant (5,19,22-23) but none of them so far has attempted to identify risk factors that might predispose to the development of ocular hypertension following Ozurdex injection.

This study aimed to analyze the pressure tolerance of Ozurdex used in “real-life” conditions. The objective was to report the incidence of OHT, analyze the pressure tolerance profile according to the different pathologies treated in this cohort study.

Materials and methods

Subjects

This study was conducted on 78 patients affected by variable degrees of macular edema. In particular, patients were affected by diabetic macular edema (DME), age-related macular degeneration (AMD), central (CRVO), and branch retinal vein occlusions (BRVO).

The intravitreal corticosteroid used in this observational study is 0.7mg dexamethasone, commercially known as 0.7mg Ozurdex®. All patients signed a consent form allowing their protected health information to be used. The demographic and clinical characteristics are shown in Table 1, Fig.1.
**Inclusion Criteria**

- Age > 18;
- Macular edema; BCVA < 45 letters on ETDRS, equivalent to a LogMAR value between 1 and 0.2 on preliminary examination;
- Central macular thickness on OCT ≥ 285 μm;
- Treatment naïve patients

**Exclusion Criteria**

- Previous laser treatments or intravitreal procedures;
- Cataract; Glaucoma; Epiretinal membrane visible on OCT;
- Any ocular surgery performed within the previous 6 months;
- Pregnancy.

**First evaluation and follow-up**

We performed all the following examinations before commencing Ozurdex® treatment: BCVA evaluation, on a decimal scale, as well as on ETDRS and logMAR scales; Slit-lamp examination and fundoscopy, Intraocular pressure measurement with Goldman applanation tonometer; Macular evaluation with OCT; Fundus photography.

Patients were re-evaluated at 1 week, 1 month and 3 months after the injection in the same fashion.

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**Pressure-lowering medications used**

Patients who developed IOP ≥ 21 mmHg were started on topical pressure-lowering medications, including: prostaglandins with or without timolol, carbonic anhydrase inhibitors with or without timolol, or an alpha2-agonist.

**Implantation Procedure**

All injections were performed in the operating room as previously described (Refs). The surgical field was sterilized with a 5% iodopovidone solution and the local anesthetic of choice was ropivacaine. Ozurdex is injected into the vitreal chamber using a disposable 22-gauge needle. All patients were given netilmicin sulfate for 10 days after the procedure.

**Safety Measures**

At each visit, patients were evaluated for complications and side-effects, such as: anterior chamber inflammation, ocular pain, keratitis, vitreous opacification, IOP increase, cataract formation and systemic side effects.

**Statistical Analysis**

Data were analyzed by ANOVA with repeated measures. Post-hoc comparisons were performed with Fisher’s Protected Least Significant Difference (PLSD) post-hoc test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software.

**Results**

**Eyes treated**

A total of 146 injections were performed on 78 patients over 3 years. 78 eyes were treated with 1 injection, 44 eyes were treated with 2 injections; 24 eyes were treated with 3 injections. Repeated injections were performed more than 3 months apart.
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Intraocular pressure (IOP) in patients treated with Ozurdex at the first injection

IOP in patients treated with Ozurdex at the first injection are shown in Fig. 2. IOP was significantly altered over time (p<0.0001), the mean IOP increase was of 1.9 mmHg. Post-hoc comparison showed that Ozurdex increased IOP at 1 week (p<0.01), 1 month (p<0.0001), and 3 months (p<0.0001) as compared to baseline.

IOP in patients treated with Ozurdex at the second injection

IOP in patients treated with Ozurdex at the second injection are also shown in Fig. 2. IOP was also significantly altered over time (p<0.0001), the mean IOP increase was of 0.23 mmHg. Post-hoc comparison showed that Ozurdex increased IOP at 1 week (p<0.0001), 1 month (p<0.0001), and 3 months (p<0.001) as compared to baseline.

IOP in patients treated with Ozurdex at the third injection

IOP in patients treated with Ozurdex at the third injection are also shown in Fig. 2. IOP was not significantly altered over time by Ozurdex (p=0.346).

Ozurdex over three years. Data are the means ± SEM. Values are expressed in mmHg. Asterisk (*) indicates significant difference between the groups. **p<0.001; ***p<0.0001.

Pressure-lowering treatment

Patients with IOP ≥ 21 mmHg (7%) were started on topical pressure-lowering medications. Monotherapy was usually effective and no laser/surgical treatment was needed to lower IOP. Furthermore, IOP spikes did not affect anyhow either visual acuity nor visual field. Similarly, no papillary changes were noticed on follow-up OCT exams.

Discussion

Cataract and ocular hypertension are the major complications of long-term use of intravitreal corticosteroids, such as dexamethasone. This complication has been reported in several observational studies, although its incidence varies. In the GENEVA study (24), 16% of participants experienced pressure spikes above 25 mmHg two months after the injection. Li X et al. (25) reported even higher incidence, where up to the 29.5% of participants were found with higher-than-normal IOP. The SAFODEX study (26) describes an incidence of 28.5%, but only about of third of them eventually required pharmacotherapy. Eter N et al (27) reports an incidence value of 13%, where 52% of the affected subjects required pressure-lowering medications. In one of our previous studies (Pacella E et al, 2017) (28) recruiting patients with retinal vein thrombosis, we observed hypertension spikes in 6% of them only. In another study treating patients with diabetic macular edema (Pacella E et al, 2016) (29), the incidence was about 15%.

Our study shows a statistically significant correlation between dexamethasone injections and IOP elevations (the mean IOP increase was of 1.9 mmHg). A second injection was correlated with an additional increase in IOP (the mean IOP increase was of 0.23 mmHg). This was also confirmed by Bahadorani S et al (2018) (30), who showed that a dose-response correlation between repeated injections and pressure spikes is noted within the 23-30 mmHg only.

In our experience, the degree of IOP elevation was often mild and was successfully treated with pressure-lowering topical medications only, permitting continuation of treatment. Otherwise no patient required laser treatment or glaucoma surgery.

In conclusion, intravitreal dexamethasone has gained progressively more popularity in the recent years for the treatment of posterior segment disease, namely macular edema due to retinal vein occlusion, diabetes, surgery and uveitis. Even though secondary OHT is a recognized complication of this treatment, it should not worry the ophthalmologist, because it can be easily managed with pharmacotherapy and regular follow-ups. Additional dexamethasone injections can be performed, if indicated.

References


