Combination of cataract surgery with intravitreal injection of dexamethasone intravitreal implant (Ozurdex) for uveitis-induced cataract

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Abstract

• AIM: To evaluate the long-term results of patients with chronic uveitis-induced cataract by phacoemulsification with IOL implantation and intravitreal injection of dexamethasone (DEX) intravitreal implant (Ozurdex).

• METHODS: The study included 32 eyes of 26 patients treated with DEX implant due to chronic uveitis-induced cataract and followed up for at least a year. Best-corrected visual acuity (BCVA), intraocular pressure (IOP), anterior chamber reaction, central macular thickness (CMT), intraoperative and postoperative complications and uveitis recurrence were analyzed retrospectively.

• RESULTS: A successful surgery was performed in all patients. The average follow-up period was 12mo. The female/male ratio was 13/13. Mean age was 45.65±3.83y (range 26 to 65y). Etiologically, rheumatic arthritis occurred in 6 patients (18.75%), ankylosing spondylitis in 4 (12.50%), HLA-B27 associated uveitis in 3 (9.38%), Vogt-Koyanagi-Harada-associated uveitis in 4 (12.50% ), Behcet’s disease in 2 (6.25%), and 7 (21.88%) suffered from unknown diseases. All 32 eyes had varying degrees of improvement at 12mo after surgery, with 2 eyes showing BCVA of 0.1 or below (6.25%), 6 having 0.1-0.5 (18.75%), 18 of 0.5-1.0 (56.25%), and 6 of 1.0 or above (18.75%). No cases with increased IOP were observed. The values of mean CMT was increased at day 1, decreased at 1, 3mo after surgery and increased at 6, 12mo-after surgery. No severe uveitis reactions, such as fibrinous exudates in the anterior chamber and exudative membrane formation on the anterior surface of the IOL, were observed after surgery.

• CONCLUSION: The present studies show that intravitreal injection of Ozudex during cataract operation can provide a new option for the clinical treatment of uveitis-induced cataract.

• KEYWORDS: uveitis-induced cataract; dexamethasone implant; intravitreal injection

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INTRODUCTION

Uveitis is one of the five leading causes of visual impairment and blindness in the developed world and causing about 20% of legal blindness. Uveitis consists anteriorly of the iris, in the middle part of the ciliary body and posteriorly of the choroid. Uveitis can be classified into anterior, intermediate, posterior and panuveitis according to the primary location of the inflammation[1]. Uveitis is the inflammation of the uveal tract, with cataract as one of the most common complications. The easy recurrence of uveitis often makes it necessary to administer high doses of glucocorticoid drugs for a long period of time pre- and postoperatively. Moreover, the long course of disease may lead to pupillary organization, and increased envelope fibrosis makes cataract surgery more difficult; coupled with serious postoperative intraocular reactions, this sometimes results in uveitis recurrence. Therefore, treating patients with uveitis-induced cataract is often challenging.

Experts in the 1990s[2-3] proposed that indications for uveitis-induced cataract surgery included uveitis-induced phacolysis, cataract-impaired vision, and uveitis under control with vision expected to be improved after surgery; fundus lesions with fundus observation and treatment affected by cataract; and vitrectomy requirement but affected by cataract. According to the Uveitis Guidelines of the Uveitis Society, experts generally believe that except for phacolysis-induced acute uveitis that requires a surgery as soon as possible, other uveitis-induced
cataract should receive active anti-inflammatory treatment and suppress intraocular inflammation for one to three months before surgery. Some experts suggested that surgeries should be performed after at least three months of intraocular inflammation suppression\cite{1-3}. Complete obliteration of anterior suspensions or mild aqueous flare are indications for intraocular inflammation suppression. To reach and maintain the state of intraocular inflammation suppression, general and/or local application of glucocorticoids is the preferred clinicians’ choice, as an effective means in controlling uveitis. According to Canada’s phacoemulsification guidelines in 2018, while performing uveitis-induced cataract surgery, most teams administer oral prednisolone (0.5-1 mg/kg, once a day) three days before surgery, in combination with local eye drops containing glucocorticoids (4 to 6 times a day)\cite{4-6} and mydriasis. This can be suspended if inflammation is curbed within one week or can be slowly reduced post-surgically based on the inflammatory response\cite{7} with the lowest dose of under 10 mg/d maintaining steady control of the inflammatory response and meanwhile glucocorticoids dropped into the eye locally. However, long-term high dose of glucocorticoids is bound to incur adverse reactions both in the eyes and all over the body\cite{8}. Timely use of immunosuppressants can effectively reduce adverse reactions caused by glucocorticoids, but long-term medication would still induce some side effects\cite{9}. Scholars have increasingly explored methods for reducing general and local use of hormones and immunosuppressants. Our institution has achieved good therapeutic effects in 26 patients (32 eyes) with chronic uveitis-induced cataract by phacoemulsification with intraocular lens (IOL) implantation and intravitreal injection of dexamethasone intravitreal implant (Ozurdex), with the following details.

**SUBJECTS AND METHODS**

**Ethical Approval** The study protocol followed the Declaration of Helsinki and was approved by Xi’an People Hospital (Xi’an No.4 Hospital). Patients provided written informed consent for participation prior to study enrolment.

**Study Design and Subjects** A total of 26 patients (32 eyes) with chronic uveitis-induced cataract administered treatment in our hospital from January 2019 to January 2020 were included. They were 13 males (15 eyes) and 13 females (17 eyes), aged between 26 and 65 (45.65±3.83)y. Inclusion criteria were: 1) oral prednisone (<20 mg/d) administration prior to uveitis diagnosis with intraocular condition stabilized for at least three months; 2) apparent lens opacity, with visual acuity below 0.1 and a high willingness to receive cataract surgery. Exclusion criteria were: 1) other intraocular surgeries; 2) active period of uveitis; 3) allergy to glucocorticoids or any excipients of Ozurdex; 4) a history of intraocular viral infection; 5) glaucoma or ocular hypertension; 6) long-term anticoagulant medication; 8) diabetes, pregnancy, or lactation.

**Preparation, Procedure and Follow-up** Medication in the perioperative period: All patients were treated with levofloxacin, pranoprofen, and tobramycin/dexamethasone eye drops three days before surgery, four times a day. Tropicamide ophthalmic was applied starting at three days before surgery, three times a day; tobramycin/dexamethasone ophthalmic were then used after surgery, four times a day for two weeks. Pranoprofen ophthalmic was applied four times a day for six weeks; tropicamide and levofloxacin eye drops were applied three and four times a day for four weeks, respectively. Operative procedures: Eye drops containing 5 g/L praracaine hydrochloride ophthalmic were administered three times for surface anesthesia ten minutes before surgery. The 2 o’clock 1 mm auxiliary corneal incision and 10 o’clock 3 mm corneal tunnel incision were adopted during the operation. Sodium hyaluronate, a viscoelastic substance, was injected into the anterior chamber, separating the posterior synechiae. Anterior continuous curvilinear capsulorhexis was then performed, alongside water separation and stratification. Lens nucleus and cortex lentis were aspirated by ultrasound emulsification, and a posterior chamber intraocular lens was implanted. Scleral tunnel needle insertion was performed at the 6 o’clock 3.5 mm corneal limbus, injecting 0.7 mg of Ozudex (Allergan Pharmaceuticals Ireland) and observing the visible white rod in the vitreous cavity. The eyes were finally sutured. Postoperative follow-up: Follow-up was performed at one day, one week, one month, three months, six months, and twelve months after surgery, respectively, with follow-up items including best-corrected visual acuity (BCVA), intraocular pressure (IOP), anterior chamber reaction examinations using slit lamp biomicroscopy, central macular thickness (CMT) measured by optical coherence tomography (OCT), intraoperative and postoperative complications and uveitis recurrence, and ophthalmic B-ultrasound examination (if necessary). The patients who received oral administration of prednisone before surgery were slowly discontinued postoperatively.

**Statistical Analysis** The data of this study was analysed using SPSS software version 20.0. Descriptive statistics presented as mean (standard deviation). The mean of CMT and IOP were analysed using ANOVA test. And categorical parameters were analysed using Chi-square test or Fisher’s exact test. Differences were considered significant at a $P$ value of <0.05.

**RESULTS**

**General Conditions** Totally 13 (50%) males and 13 (50%) females, aged 45.65±3.83 (26 to 65y), were assessed. There were 6 cases with anterior uveitis, 5 with intermediate uveitis, 8 with posterior uveitis, and 7 with panuveitis. Etiologically, 6 (18.75%) patients had rheumatic arthritis, 4 (12.50%) had...
ankylosing spondylitis, 3 (9.38%) had HLA-B27 associated uveitis, 4 (12.50%) had Vogt-Koyanagi-Harada-associated uveitis, 2 (6.25%) had Behçet’s disease, and 7 (21.88%) suffered from unknown diseases.

**Best-corrected Visual Acuity** All 32 eyes had varying degrees of improvement at 12mo after surgery, with 2 eyes showing BCVA of 0.1 or below (6.25%), 6 having BCVA of 0.1-0.5 (18.75%), 18 displaying BCVA of 0.5-1.0 (56.25%), and 6 having BCVA of 1.0 or above (18.75%). The number of BCVA degrees categorical parameters were analysed using Chi-square test ($\chi^2=92.403$, $P<0.001$; Table 1).

**Intraocular Pressure** IOP in the subjects improved from 9.4-18.2 mm Hg (14.32 mm Hg on average) before surgery to 10.2-16 mm Hg (13.54 mm Hg on average) thereafter. No cases with increased IOP were observed. The values of mean was not statistically significant ($F=0.607$, $P>0.05$; Table 1).

**Ocular Anterior Segment Reactions** Patients with preoperative synechiae had more pronounced anterior chamber reactions postoperatively, while the remaining subjects had mild anterior segment reactions. Anterior chamber cells and aqueous flare changes in patients after surgery reduced after a week and disappeared after a month. No severe uveitis reactions, such as fibrinous exudates in the anterior chamber and exudative membrane formation on the anterior surface of the IOL, were observed after surgery (Figure 1, Table 2).

**Optical Coherence Tomography** The values of mean CMT from preoperatively to postoperatively are shown in Table 1 and Figure 2. The OCT results of 7 eyes in all eyes were not available because of thick opacity of cataract, so they were not included in the statistics. The values of mean CMT was increased at 1wk, decreased at 1, 3mo after surgery and increased at 6, 12mo after surgery, and it was statistically significant ($F=4.462$, $P<0.001$; Table 1, Figure 2).

**Complications and Management** All patients had a successful surgery, without posterior capsule rupture or serious complications such as hemorrhage and infection perioperatively. A total of 2 cases had mild corneal edema the day after surgery, but recovered after a week. Totally 5 cases showed posterior capsular opacification at reexamination three
months after surgery, and underwent YAG laser capsulotomy six months postoperatively. Two cases had epiretinal membranes after surgery, and were subsequently placed in temporary observation. There were no cases of surgically induced macular edema. One case showed macular edema induced by epiretinal membranes at reexamination ten months after surgery, and received surgical treatment. No uveitis recurrence was observed during the follow-up period.

**DISCUSSION**

As one of the diseases causing blindness, uveitis has hundreds of causes, but the associated etiological mechanism remains undefined, making treatment challenging; cataract is the most common complication[1]. Patients with anterior uveitis or intermediate uveitis experience repeated recurrence and long-term inflammatory response that leads to inflammatory cell infiltration to the lens capsule, affecting its permeability, with altered composition of aqueous fluids affecting lens metabolism that causes the cataract complication; meanwhile, patients with posterior uveitis develop cataract as a result of long-term intake of glucocorticoid drugs in addition to inflammatory causes[9]. The preferred surgical method for uveitis-induced cataract is phacoemulsification in conjunction with IOL implantation. However, due to synechiae, pupillary membrane, iridoileptysis, and iris hemorrhage in uveitis patients, uveitis-induced cataract surgery is more difficult than conventional cataract surgeries, and easily causes inflammation recurrence after surgery, as well as complications such as synechiae, anterior lens membrane, posterior capsular opacification, and macular edema, making it hard to maintain normal vision after surgery[2,10]. Therefore, this study intends to find a more suitable treatment for uveitis-induced cataract, hoping to better improve the vision of patients, reduce postoperative reactions, prevent postoperative macular edema, maintain or even reduce CMT, and reduce the recurrence of uveitis. İşik and Yalçındag[11] found that nepafenac 0.1% is effective in suppressing inflammation after cataract surgery in uveitic eyes as well as in healthy eyes. Alkawas et al.[12] achieved good anti-inflammatory effects while combining uveitis-induced cataract surgery with intravitreal injection of triamcinolone acetonide, but many patients had ocular hypertension after surgery. Chieh et al.[13] discovered that fluocinolone acetonide intravitreal implant (Retisert) used in conjunction with uveitis-induced cataract surgery could improve visual acuity and reduce the general use of immunosuppressants and uveitis recurrence. Retisert was the first fluocinolone acetonide used for treating chronic non-infectious uveitis with abiotic degradation of delivery systems for intraocular implantation. Multiple studies suggested that Retisert implantation can effectively reduce the general use of glucocorticoids and uveitis recurrence, but often causes postoperative cataract and ocular hypertension as well as non-surgical complications such as implantation system discharge. Causing many ocular and surgical complications, it is less applied clinically. Arcinue et al.[14] found that Ozudex performs better than Retisert in terms of controlling inflammation development, improving visual acuity, and preventing uveitis recurrence. The BCVA of the patients in this study has been improved to varying degrees. It is considered that the opaque lens was removed, and the opacity of the lens is the main reason for the impact on BCVA of the patients in this study. This study also found that the postoperative anterior chamber cells and aqueous flare were relatively heavier at day 1 postoperatively, which was significantly reduced at 1wk postoperatively, and disappeared at 1mo postoperatively. No patients had serious complications such as iris synechiae. Hence, Ozudex not only prevents glucocorticoids-associated IOP increase, but also avoids general side effects caused by the local use of glucocorticoids and the general use of glucocorticoids or immunosuppressants. This study found that one eye of a patient developed ocular hypertension at day 1 postoperatively that resolved by the next follow up visit. Therefore, intraoperative use of Ozurdex can greatly reduce the occurrence of uveitis and secondary glaucoma, and Ozuredx is used as a sustained release agent, can achieve the effect of stabilizing IOP. As the first biodegradable dexamethasone drug delivery system approved by the FDA, Ozurdex is used to treat non-infectious uveitis[1,15-20], and contains the copolymer poly (lactic-co-glycolic-acid) and 700 µg micronized dexamethasone. It can be six months, inhibiting multiple inflammatory markers to reduce macular edema, fibrin deposition, capillary leak, and inflammatory cell migration. Previous studies on Ozurdex were mostly used for the study of macular edema secondary to uveitis. After using Ozurdex, CMT decreased by 120 µm at 1mo postoperatively and showed a significant half-life at 3mo postoperatively[1]. An

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**Figure 2** Graph showing trend of central macular thickness (µm) on various follow-up visit.
experimental study found that following intravitreal Ozurdex injection, dexamethasone was detectable in retina and vitreous even 6mo after administration, achieving peak concentrations during the first 2mo\textsuperscript{[1]}. The results of this study are similar to before study. The CMT decreased most significantly at 1 and 3mo postoperatively, and the CMT increased again at 6mo postoperatively. In this study, CMT increased slightly at day 1 postoperatively, which is considered to be related to the stimulation during surgery. However, the 12mo follow-up showed that there was no significant macular edema in this study. Since its delivery materials are biodegradable, Ozudex can substantially reduce surgical complications. Therefore, we combined phacoemulsification and IOL implantation with intravitreal injection of Ozurdex to treat uveitis-induced cataract, and patients administered oral prednisone before surgery gradually reduced their medication doses till drug withdrawal and only received local treatment of anti-inflammatory ophthalmic, with good therapeutic effects. All patients that received the treatment had no ocular hypertension after surgery, with stable IOP and no statistical difference compared to pre-surgical conditions. Postoperative visual acuity improved to varying degrees, and postoperative anterior chamber reactions were mild. No patients had fibrous membrane exudation caused by severe anterior chamber reactions. All patients had stable fundus conditions and none suffered from postoperative macular edema. During follow-up visits, no patients had uveitis recurrence, which demonstrated the prominent therapeutic effects of intravitreal injection of dexamethasone intravitreal implant for treating uveitis-induced cataract, including effective reduction of uveitis recurrence and safe and effective prevention of postoperative macular edema. To sum up, uveitis-induced cataract is a common complication of uveitis that can severely affect visual acuity and medical observation of the ocular posterior segment. Performing phacoemulsification with IOL implantation at an appropriate time can remove cataract occlusion and improve patient’s visual acuity. However, as uveitis-induced cataract surgery is unique in some ways, pre-surgical intraocular inflammation is required for stabilization for at least three months. In addition, anti-inflammation is quite important in the perioperative period, when complex operations require more skillful techniques. Given many postoperative complications, simultaneous intravitreal injection of Ozudex can effectively relieve postoperative reactions, reduce uveitis recurrence, and safely and effectively prevent postoperative macular edema. Studies have shown that intravitreal injection of Ozudex can provide a new option for the clinical treatment of uveitis-induced cataract. However, this study is a retrospective case analysis. Since the control group was not included in this study, it is hoped that it will be further explored in future studies. In addition, a larger sample size and long-term follow-up are needed to determine its long-term efficacy. The follow-up period should be extended to observe long term postoperative reactions including macular changes in future studies. Further multi-center large sample study by different tertiary centers would be necessary to analyze the beneficial effects of intravitreal injection of Ozudex on different subtypes of uveitis.

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Conflicts of Interest: Deng J, None; Sun WT, None; Ai H, None; Wang LP, None.

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