



Efficacy of vitrectomy combined with an intraoperative dexamethasone implant in refractory diabetic macular edema

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Abstract

Aims To evaluate the safety and efficacy of vitrectomy combined with an intraoperative dexamethasone (Ozurdex[®]) implant in refractory diabetic macular edema (DME).

Methods Patients who were diagnosed at our institution as having DME refractory to more than 6 months of non-surgical treatment and underwent intravitreal dexamethasone implantation combined with vitrectomy. All patients were followed up for more than 12 months. Best-corrected visual acuity (BCVA, logMAR), central macular thickness (CMT), and intraocular pressure at the initial visit and 1, 3, 4, 6, and 12 months after treatment were recorded.

Results Twenty-two eyes (22 patients) were included in this study. The mean preoperative BCVA was 0.68 and the mean CMT was 470.80 μm . The total number of the previous injections was 5.1 ± 1.6 . The mean BCVA was significantly improved at all visits, and the mean CMT was also significantly reduced ($p < 0.05$). Sixteen eyes (73%) did not need additional implantations during follow-up.

Conclusions Vitrectomy combined with an intraoperative dexamethasone (Ozurdex) implant was an effective and safe treatment option in patients with refractory DME.

Keywords Dexamethasone implant · Ozurdex[®] · Vitrectomy · Diabetic macular edema

Introduction

Diabetic macular edema (DME) is a common cause of visual impairment in patients with diabetic retinopathy and occurs in approximately 10% of diabetic patients and 29% of those with a disease duration of more than 20 years [1].

In the Early Treatment Diabetic Retinopathy Study, focal and grid photocoagulation procedures were reported to be effective in DME. However, by 3 years after treatment, macular edema had recurred in 24% of patients and the prognosis was particularly poor in eyes with diffuse macular edema [2, 3]. Intravitreal anti-vascular endothelial growth factor (VEGF) injection is effective therapy for DME, but not effective in all DME patients and requires frequent injection [4]. Triamcinolone is also an effective drug for DME.

However, it is difficult to use because of its troublesome side effects, which include endophthalmitis, progression of cataract, and elevation of intraocular pressure (IOP) [5, 6].

Vitrectomy may be considered in patients with DME that is refractory or persistent despite laser or intravitreal injection. Vitrectomy with internal limiting membrane (ILM) peeling can relieve macular edema by reducing traction between the vitreous and retina and by decreasing the levels of cytokines or growth factors in the vitreous that increase vascular permeability [7–10]. However, there have been reports of persistent or recurrent macular edema after vitrectomy [10] and the clearance rate from the vitreous cavity may increase after vitrectomy, leading to shortening of the drug's half-life. Therefore, frequent reinjections may be required [11].

Ozurdex[®] (Allergan Inc., Irvine, CA, USA) is a biodegradable implant that gradually releases low-dose dexamethasone for several months after being injected into the vitreous cavity and can maintain dexamethasone above a certain concentration for 3–6 months. Furthermore, the side effects that tend to appear with frequent injections, such as endophthalmitis, cataract, and elevation of IOP, are reduced

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[12]. Gillies et al. reported that the number of injections of dexamethasone required to improve visual acuity (VA) in patients with DME was smaller than that required with bevacizumab [13]. There are also several reports of the dexamethasone intravitreal implant being effective for persistent DME [14–16]. In particular, prolonged drug release from a dexamethasone implant after vitrectomy can be expected to improve refractory DME.

Thus, we review the medical records of patients who had a history of refractory DME and assess the results achieved by an intravitreal dexamethasone (Ozurdex) implant combined with vitrectomy.

Materials and methods

We retrospectively reviewed our medical records to identify patients who had a history of DME refractory to non-surgical treatment for more than 6 months from October 2014 to April 2016. The study was approved by the Institutional Review Board of Konyang University Hospital, Daejeon, South Korea (KYUH 2017-08-002) and followed the principles of the Declaration of Helsinki.

The outcome measures were best-corrected visual acuity (BCVA), IOP and central macular thickness (CMT) measured on spectral-domain optical coherence tomography (Heidelberg Spectralis[®], Heidelberg Engineering, Heidelberg, Germany) at baseline and at 1, 3, 4, 6, and 12 months after treatment.

DME defined clinically and by $CMT \geq 300 \mu\text{m}$ measured by optical coherence tomography. The inclusion criteria were refractory or persistent DME despite the previous non-surgical treatments, including laser, intravitreal anti-VEGF, or steroid injection or sub-tenon triamcinolone injection, for more than 6 months and Snellen BCVA ≤ 0.5 . The exclusion criteria were as follows: treatment for DME in the study eye within the previous 3 months; a history of intravitreal dexamethasone implantation to treat DME; a history of cataract surgery in the study eye within the previous 6 months; a vitrectomized eye; significant visual loss ($< 20/40$) attributable to severe cataract, corneal disease or optic nerve disease; a history of glaucoma; a history of or active ocular infection or inflammation in the study eye; and a history of any retinal disease that might further compromise VA, such as age-related macular degeneration, retinal vein occlusion, or retinal detachment.

All surgeries were performed under retrobulbar anesthesia by 1 surgeon (YH Lee), and involved 25-gauge transconjunctival sutureless vitrectomy (TSV25) with a Constellation[®] vision system (Alcon, Fort Worth, TX, USA) and Ultravit[®] 25-gauge plus (Alcon) vitrectomy instruments. In all eyes, the ILM was stained with 0.25% indocyanine green (LDS Pharm Co., Ltd, Seoul, Korea)

and peeled carefully to a radius of 2–3 disc diameters using an intraocular forceps. Just before the end of the surgery, a 0.7-mg dexamethasone implant was placed into the vitreous cavity using a single-use applicator with a 22-gauge needle. Cataract surgery was performed simultaneously as needed.

The BCVA was measured using a Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR) for the statistical analysis. During follow-up, the dexamethasone implant was re-injected if the CMT increased by $> 300 \mu\text{m}$ or the BCVA decreased by more than two lines. Changes in the preoperative and postoperative BCVA, CMT, and IOP were assessed for statistical significance using the Wilcoxon's signed-rank test. Binary logistic regression model was established to investigate factors affect to re-treatment. The threshold for statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

Total 22 patients (22 eyes) were included in this study. The demographic and clinical characteristics of the patients and study eyes at baseline are listed in Table 1. The mean age of the patients was 59.13 years and the mean duration of diabetes was 12.60 years. The mean HbA1c of the patients was 7.42%. Fourteen of the 22 eyes were pseudophakic. The mean numbers of the previous treatments with intravitreal bevacizumab, posterior sub-tenon triamcinolone, and intravitreal triamcinolone were 3.4, 1.1, and 0.5, respectively. The total number of the previous injections was 5.1 ± 1.6 . The mean preoperative BCVA (logMAR) was 0.68 and the mean CMT was $470.80 \mu\text{m}$ (Table 1).

Visual and anatomical outcomes

The mean BCVA (logMAR) was improved to 0.39 ± 0.16 , 0.36 ± 0.18 , 0.37 ± 0.18 , 0.40 ± 0.15 , and 0.37 ± 0.19 at 1, 3, 4, 6, and 12 months, respectively ($p < 0.05$; Fig. 1a). The mean change in BCVA was -0.30 ± 0.20 , -0.32 ± 0.19 , -0.32 ± 0.22 , -0.29 ± 0.21 , and -0.32 ± 0.25 at 1, 3, 4, 6, and 12 months (Fig. 1b). The mean CMT was $342.47 \pm 46.72 \mu\text{m}$, $303.20 \pm 54.95 \mu\text{m}$, $334.07 \pm 61.86 \mu\text{m}$, $331.87 \pm 53.20 \mu\text{m}$, and $353.33 \pm 68.91 \mu\text{m}$ at 1, 3, 4, 6, and 12 months. It showed a statistically significant reduction in CMT when compared with the preoperative CMT ($p < 0.05$; Fig. 2a). The mean change in CMT was -128.33 ± 72.66 , -167.60 ± 95.50 , -136.73 ± 102.30 , -138.93 ± 85.98 , and -117.47 ± 62.08 at 1, 3, 4, 6, and 12 months (Fig. 2b).

Table 1 Patient demographics and clinical characteristics

Patients (eyes)	22 (22)
Age (years)	59.1 ± 9.1
Sex (male:female)	13:9
Type of DM (type 1: type 2)	0:22
Duration of diabetes (years)	12.6 ± 6.2
HbA _{1c} (%)	7.4 ± 1.8
Treatment of DM	
Insulin	9
Oral antihyperglycemic agents	5
Mixed	8
Presence of hypertension	14
Mean diastolic pressure	72.5 ± 7.2
Mean systolic pressure	118.3 ± 9.7
Presence of dyslipidemia	18
Use of statins	18
Lens type	
Phakic	8
Pseudophakic	14
Previous injection	5.1 ± 1.6
IVB	3.4 ± 1.1
STTA	1.1 ± 1.0
IVTA	0.5 ± 0.7
Preoperative BCVA (logMAR)	0.68 ± 0.15
Preoperative CMT (μm)	470.8 ± 77.4
Preoperative IOP (mmHg)	15.4 ± 2.3
Severity of DR (ETDRS grading)	
Severe NPDR	12
PDR	10
Panretinal photocoagulation	
Yes	16
No	6

The data are shown as the mean and standard deviation unless otherwise indicated

DM diabetic mellitus, BCVA best-corrected visual acuity, CMT central macular thickness, DR diabetic retinopathy, HbA_{1c} glycated haemoglobin, IOP intraocular pressure, IVB intravitreal bevacizumab injection, IVTA intravitreal triamcinolone acetonide injection, log-MAR logarithm of the minimum angle of resolution, NPDR non-proliferative diabetic retinopathy, PDR proliferative diabetic retinopathy, STTA sub-tenon injection of triamcinolone acetonide

Numbers of dexamethasone re-implantations

Sixteen eyes (73%) did not need additional implantations during follow-up. The mean number of dexamethasone re-implantations was 0.4 ± 0.8. Binary logistic regression analysis was performed to identify factors affecting dexamethasone re-implantation. Age, sex, duration of diabetes, HbA_{1c}, hypertension, dyslipidemia, preoperative BCVA, preoperative CMT, initial severity of DR, and PRP status were incorporated into the analysis. None of these variables affected re-treatment.

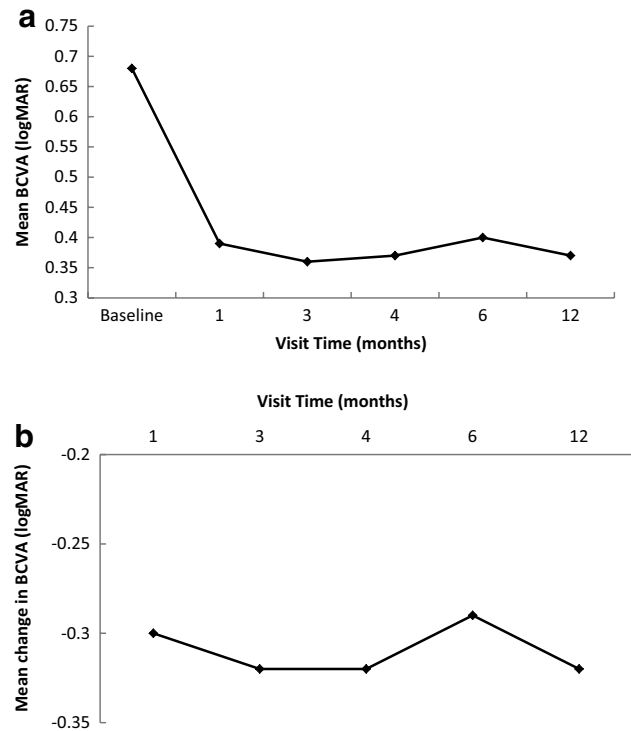


Fig. 1 **a** Mean best-corrected visual acuity (BCVA) and **b** mean change in BCVA

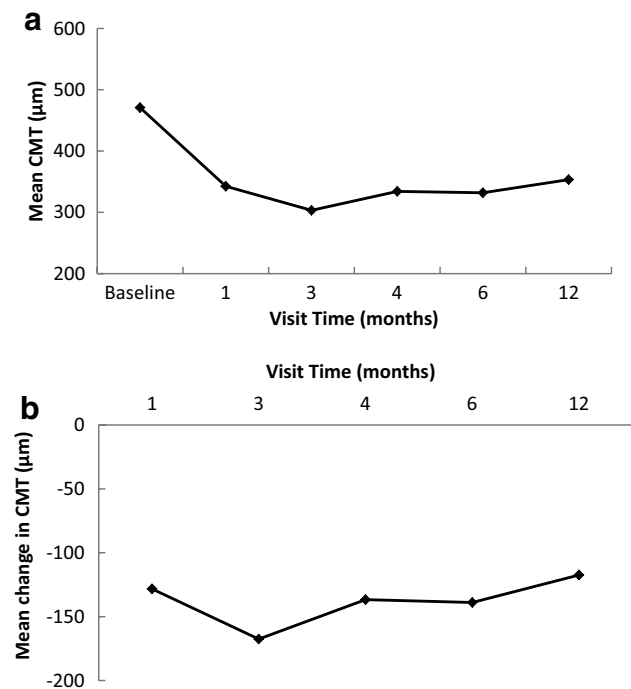


Fig. 2 **a** Mean central macular thickness (CMT) and **b** mean change in CMT

Safety outcomes

Two eyes (9.1%) showed an increase in IOP (≥ 25 mmHg) at 1 month that reverted to normal after use of an IOP-lowering eyedrop [Cosopt® (Merck & Co., Inc., Kenilworth, NJ, USA)]. No other complications were observed during routine follow-up.

Discussion

Focal and grid photocoagulation has been widely used as a treatment for DME. It is an effective treatment for localized macular edema but less effective for diffuse or cystoid macular edema. In one study, VA improved in only 17% of cases after treatment [3]. Beck et al. reported that more than 15 letters of visual loss were observed in 12% of cases during 3 years of follow-up [17]. Furthermore, adverse effects such as choroidal neovascularization and submacular fibrosis were reported after laser treatment. Therefore, the need for better treatment modalities for refractory DME was recognized.

At present, the most common treatment for DME is intravitreal anti-VEGF injection. In patients with DME, the concentration of intravitreal VEGF is increased in proportion to the severity of the macular edema [18]. The Diabetic Retinopathy Clinical Research Network (DRCR.net) reported a clinically significant decrease in macular thickness at 3–6 weeks after intravitreal bevacizumab injection [19]. However, in a rabbit model, the mean half-life of bevacizumab was 4.32 days after intravitreal injection [20]. Therefore, intravitreal bevacizumab injection has the limitation of needing to be repeated within a relatively short period of time.

Triamcinolone, which was used widely to treat DME prior to anti-VEGF injection, inhibits the arachidonic acid pathway, thereby inhibiting production of the prostaglandins that trigger an inflammatory response. In addition, triamcinolone inhibits production of VEGF and has a potent anti-inflammatory effect on macular edema by inhibiting vascular proliferation and reducing vascular permeability [21]. However, in the study conducted over a period of 3 years by DRCR.net, the rate of adverse effects, including cataract, was high and visual improvement was less than that in a laser treatment group [17].

Dexamethasone is a steroid that exerts potent anti-inflammatory effects via several mechanisms, including reducing vascular permeability, inhibiting fibrin deposition, and migration of white blood cells and inflammatory cells, stabilizing endothelial cell adhesion, and inhibiting synthesis of VEGF, prostaglandins, and other cytokines. Dexamethasone is five times more potent than triamcinolone and can exist in a high concentration in the vitreous because of its

high hydrophilicity. Furthermore, it has the advantage of not causing blurring or vitreous floaters after injection [22]. Moreover, because of its short half-life of 3 h, it is less effective after intravitreal injection. However, the recently developed intravitreal dexamethasone (Ozurdex) implant can overcome this limitation by maintaining the concentration of dexamethasone above a certain level in the vitreous cavity for 3–6 months. Ozurdex can be used safely because it decomposes slowly in the vitreous cavity into carbon dioxide and water [23]. Pacella et al. reported significant improvement in VA for 4 months and a decrease in CMT for 6 months after Ozurdex implantation in eyes with DME refractory to laser photocoagulation, intravitreal anti-VEGF, and steroid injections [12]. Gillies et al. reported a significantly greater decrease in CMT in an Ozurdex implant group than in an intravitreal bevacizumab injection group and that the Ozurdex implant group required a mean of 2.7 injections per year compared with 8.6 injections in the bevacizumab group [13]. Catharina et al. reported eyes with DME considered refractory to anti-VEGF therapy after 3 monthly injections which were switched to ozurdex implant and had better visual and anatomical outcomes at 12 months than those that continued treatment with anti-VEGF therapy in a real-world setting [16].

Vitreotomy could be an alternative treatment for refractory DME. The mechanisms by which DME is postulated to improve after vitrectomy include a reduction of vitreomacular traction, removal of VEGF, and improved transvitreal oxygenation of the retina [8]. Rosenblatt et al. reported that vitrectomy and ILM peeling were effective treatments for refractory DME [7]. However, even after vitrectomy, there are some patients in whom there is no significant improvement in VA or a recurrence of macular edema. Therefore, vitrectomy combined with an intraoperative dexamethasone implant may help to improve the prognosis.

After vitrectomy, the vitreous is replaced with an aqueous humor that has lower viscosity than normal vitreous. In a vitrectomized eye, as the circulation increases in the vitreous cavity, agents such as anti-VEGF and triamcinolone are widely distributed and rapidly removed, leading to increased drug clearance and a short half-life. Lee et al. reported that drug clearance was 2.49 mL/h in a vitrectomized eye and 0.564 mL/h in a non-vitrectomized eye and that the clearance rate in a vitrectomized eye was about four times higher than that in a non-vitrectomized eye [11]. Ozurdex slowly releases dexamethasone over a period of months after injection, so may be a useful option for vitrectomized eyes.

In this study, the ILM was removed in all patients. Yu et al. suggested that the ILM may exert tractional forces on the macula, so peeling of the ILM with vitrectomy may be more effective than vitrectomy alone [24]. However, some authors insist that ILM peeling is not an important factor in DME without macular traction [10, 25]. We suspect that

the ILM in patients with diabetes may be associated with macular traction and may function as a scaffold for proliferating astrocytes; therefore, we performed ILM peeling with vitrectomy. In addition, ILM peeling may facilitate penetration of dexamethasone into the retinal tissue by removing a mechanical barrier.

BCVA and CMT were significantly improved up to 12 months after treatment in this study. Lazic et al. reported that BCVA and CMT improved until 3 months after injection, but after that, the treatment effect decreased and the BCVA and CMT at 4 months were similar to those before the treatment [14]. Marco et al. reported improvement in BCVA and CMT until 6 months after ozurdex injection, but the effect decreased slightly after 3 months of treatment [15]. Ozurdex is known to persist for up to 3 months after injection and gradually decrease until 6 months following the injection [11, 12]. Therefore, repeated injection was required to many patients [12–15]. However, as already reported by Lee et al. [26], our study showed statistically significant improvements in VA and CMT during a year of follow-up. Furthermore, 16 eyes (73%) did not require re-treatment for 12 months. Therefore, vitrectomy combined with an intraoperative dexamethasone implant has the advantage of not only improving BCVA and CMT but also requiring fewer additional injections, which may reduce the risk of intraocular complications associated with frequent injections and be more beneficial in terms of convenience to the patient and financial cost. In addition, intravitreal dexamethasone implant can reduce peripheral retina ischemia in patients with DR and has the potential to not only delay progression of DR and PDR development, but may also improve DR severity over 24 months [27, 28]. These facts can serve potential advantage.

Our study has several limitations in that it had a retrospective design, a relatively short follow-up period, and a small study population that precluded any estimation of long-term efficacy or safety. In addition, we tried to find the factors related to re-treatment through regression analysis, but we could not find any particular association. This is probably due to a small number of patients. Furthermore, the changes in VA after treatment may have been affected in patients with phakic refractory DME, even though the cataracts were not severe. These variables should be controlled for in longer term, larger scale, prospective studies in the future.

In conclusion, our findings demonstrate that vitrectomy combined with intraoperative dexamethasone implantation may produce a clinically meaningful and statistically significant benefit in the treatment of refractory DME. This treatment strategy may have the additional benefit of entailing fewer repeat intravitreal injections, thereby decreasing side effects and increasing patient convenience.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board of Konyang University Hospital, Daejeon, South Korea (KYUH 2017-08-002) and followed the principles of the Declaration of Helsinki.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent None.

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