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Therapeutic effect of cataract surgery with simultaneous intravitreal injection of aflibercept on diabetic macular edema

An observational study

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Abstract

This study aimed to investigate the therapeutic effect of cataract surgery along with simultaneous intravitreal injection (IVI) of aflibercept on diabetic macular edema (DME). This cohort study enrolled 106 patients aged >40 years with type 2 diabetes mellitus and DME who received cataract surgery from January 1, 2016, to October 31, 2020. The baseline and mean data of the following parameters were collected: age, sex, glycated hemoglobin level, diabetic retinopathy (DR) grading, previous DR treatments including IVI of anti–vascular endothelial growth factor and pan-retinal photocoagulation, intraocular pressure, use of intraocular pressure-lowering medication, central subfield thickness (CST), and log MAR visual acuity (VA). Patients were categorized into 2 groups based on whether they received aflibercept IVI or not during cataract surgery and were compared using the *t* test and Fisher exact test for continuous and discrete variables, respectively. Beta coefficient and standard error were calculated using multiple linear regression analysis to identify the explanatory variables predictive of the net change of CST and log MAR VA. There was no difference in the net change in CST (15.24 ± 45.07 μm vs 18.62 ± 33.84 μm, $P = .772$) and log MAR VA (–0.27 ± 0.29 vs –0.37 ± 0.31, $P = .215$). Gender, glycated hemoglobin level, aflibercept IVI during cataract surgery, and baseline CST did not interfere with the morphological and functional outcomes of DME in cataract surgery. Older age was significantly and independently associated with a greater net change in log MAR VA. Proliferative DR was significantly and independently associated with a greater net change in CST and log MAR VA. A greater baseline log MAR VA was significantly and independently associated with lower net change in log MAR VA. Simultaneous aflibercept IVI for treating DME may not interfere with the functional and tomographic parameters of cataract surgery relative to cataract surgery alone. Factors influencing the outcomes of patients with DME undergoing cataract surgery are as follows: age, baseline DR staging, and baseline VA. Identifying these factors of DME preoperatively may be an important consideration in preventing it from progressing and for improving the overall visual prognosis.

Abbreviations: BRB = blood–retina barrier, CST = central subfield thickness, DM = diabetes mellitus, DME = diabetic macular edema, DR = diabetic retinopathy, HbA1c = glycated hemoglobin, IOP = intraocular pressure, IVI = intravitreal injection, NPDR = nonproliferative DR, PDR = proliferative DR, PRP = pan-retinal photocoagulation, VA = visual acuity, VEGF = vascular endothelial growth factor.

Keywords: anti–vascular endothelial growth factor, cataract surgery, central subfield thickness, diabetic macular edema, diabetic mellitus, intravitreal injection, visual acuity

1. Introduction

Diabetic retinopathy (DR) is one of the leading causes of visual loss worldwide. At present, more than 93 million people are affected, of which one-third have vision-threatening DR.[1,2] Diabetic macular edema (DME), which is attributed to retinal barrier rupture secondary to angiogenesis and inflammation, is one of the major causes of visual impairment in DR.[3] This

Informed consent was obtained from all subjects involved in the study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Taipei City Hospital (IRB No.: TCHIRB- 11003029-E).

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condition may cause irreversible damage of the macula and permanent vision loss if left untreated.[4] The aim of DME treatment is based on 2 aspects:

1. reduction of the vascular endothelial growth factor (VEGF) level, through either intravitreal injection (IVI) of anti-VEGF drug or retinal photocoagulation, and
2. inflammation control, primarily through IVI of steroids and its derivatives.[5–9]

Previous studies revealed that inflammation associated with cataract surgery may exacerbate the breakdown of the blood–retina barrier (BRB), which could worsen DR and DME.[10–12] The Diabetic Retinopathy Clinical Research Network also implicated that cataract surgery may increase the risk of developing DME and worsening visual acuity (VA) within 16 weeks of cataract extraction.[13] In addition, the costs of treating DME following cataract surgery could be extremely high, at US$10,410 in average.[14] In clinical practice, patients with DME who are prescribed cataract surgery commonly received IVI of an anti-VEGF drug preoperatively.[15,16] Although the therapeutic effect of cataract surgery with simultaneous IVI of anti-VEGF had been well studied, most of them focused on ranibizumab or bevacizumab and evaluating other macular disorders such as age-related macular degeneration.[17] The present study aims to investigate the therapeutic effect of cataract surgery with simultaneous IVI of aflibercept on DME.

2. Methods

2.1. Participants

This single-center observational study was approved by the Research Ethics Committee of Taipei City Hospital, Taiwan (TCHIRB-11003029-E) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient. Candidates of this study were patients aged over 40 with type 2 diabetes mellitus (DM) and DME, who underwent cataract surgery in Taipei City Hospital Renai Branch, Taiwan from January 1, 2016, to October 31, 2020. DM was defined as either fasting blood sugar ≥126 mg/dL, self-report of physician-diagnosed DM, or the use of hypoglycemic medications. DME was defined as 1 or more of the following according to Early Treatment of Diabetic Retinopathy Study criteria: retinal thickening at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula, if associated with adjacent retinal thickening; or a zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the center of the macula.[18] All patients had baseline glycated hemoglobin (HbA1c) <10% (mmol/mol) following Taiwan health insurance regulations for IVI of anti-VEGF, and patients with epiretinal membrane or tractinal maculopathy were excluded. All cataract surgeries were performed by a single surgeon, with phacoemulsification and posterior-chamber intraocular ocular lens implantation in the capsular bag without any posterior capsular tear or any other intra- or postoperative complications. Cataract surgery and IVI of 2 mg aflibercept (0.05 mL) were performed concurrently in study group. The control group only received treatment with cataract surgery. In either study or control group, there were no local or systemic adverse events in the 3-month observation period. All patients received baseline examination and regular follow-up for assessment 3 months after operation. Patients who lost to follow-up were excluded in this study.

2.2. Clinical data and potential factors

Baseline factors evaluated were age, sex, HbA1c level, DR grading, previous DR treatments including anti-VEGF IVI and pan-retinal photocoagulation (PRP), intraocular pressure (IOP), use of IOP-lowering medication, central subfield thickness (CST), and log MAR VA. HbA1c level was measured using high-performance liquid chromatography (Bio-Rad Laboratories, Inc, Hercules, CA.). The diagnosis of DR was based on fundus photography centered on the fovea, obtained using a fundus camera (CanonCR-2; Canon, Tokyo, Japan). Images were graded into no DR, mild/moderate/severe nonproliferative DR (NPDR), and proliferative DR (PDR) in accordance with the International Clinical DR severity scales.[19] Eligibility was determined by 2 ophthalmologists (P.-C.T. and C.-Y.Y.), who evaluated retina appearance on fundus photographs to reach a consensus. Both the evaluators were blinded to all other patient and ocular data. For patients with gradable imaging results for both the eyes, the more severe one was recorded. Patients were considered treatment naive if they had not received anti-VEGF IVI or had not undergone PRP. IOP was measured in millimeter of mercury (mmHg) using a noncontact tonometer (Topcon CT-80; Topcon, Tokyo, Japan). CST was measured in μm using RTVue optical coherence tomography (Optovue Inc., Fremont, CA). Log MAR VA was evaluated by measuring the distance best-corrected VA under normal luminance with a log MAR VA chart at a distance of 6 m (20 feet). A larger value of log MAR VA indicated poorer VA, whereas a smaller value of log MAR VA indicated better VA. The net change in CST and log MAR VA was calculated by subtracting the value obtained at follow-up and that obtained at baseline.

2.3. Statistical analysis

SPSS version 22.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. Patients were divided into 2 groups based on whether or not they received aflibercept IVI during cataract surgery. Baseline characteristics were reported as counts and proportions or means ± standard deviations, as appropriate. The 2 groups were compared using *t* test and Fisher exact test for continuous and discrete variables, respectively. Beta coefficient and standard error were calculated using multiple linear regression analysis to identify the explanatory variables predictive of the net change in CST and log MAR VA. The explanatory variables were age, sex, HbA1c level, DR status, previous DR treatments including anti-VEGF IVI and PRP, aflibercept IVI administered during surgery, IOP, use of IOP-lowering medication, CST, and log MAR VA. Statistical significance was considered at $P < .05$.

3. Results

Of the 134 patients in this cohort, 9 had ungradable or unrecorded fundus images or clinical lab data, and 13 were lost to follow-up 3 months later. Among the patients with data during follow-up, 6 had unrecorded fundus images or clinical lab data. Finally, 106 patients were included in this study (Fig. 1).

3.1. Factors associated with DME

Characteristics of the included subjects (N = 106) are presented in Table 1. The mean age was 68.76 ± 9.09 years. A total of 17 (16.04%) patients underwent cataract surgery and received 2 mg aflibercept IVI (study group) and 89 (83.96%) underwent only cataract surgery (control group). Patients in the study group had more severe baseline DR staging (41.18% had mild NPDR, 23.53% had moderate NPDR, and 35.9% had PDR); in contrast, patients in the control group had mild baseline DR staging (53.3% had no DR, 13.48% had mild NPDR, 17.98% had moderate NPDR, and 14.61% had PDR). More patients are treatment naive in the control group (80.90%) than in the study group (47.06%). More patients received PRP in the study group (41.18%) than in the control group (16.85%). There was no difference in the baseline CST (341.20 ± 40.69 μm vs 339.80 ± 24.63 μm, $P = .573$), baseline log MAR VA (0.50 ± 0.30 vs 0.50 ± 0.32,

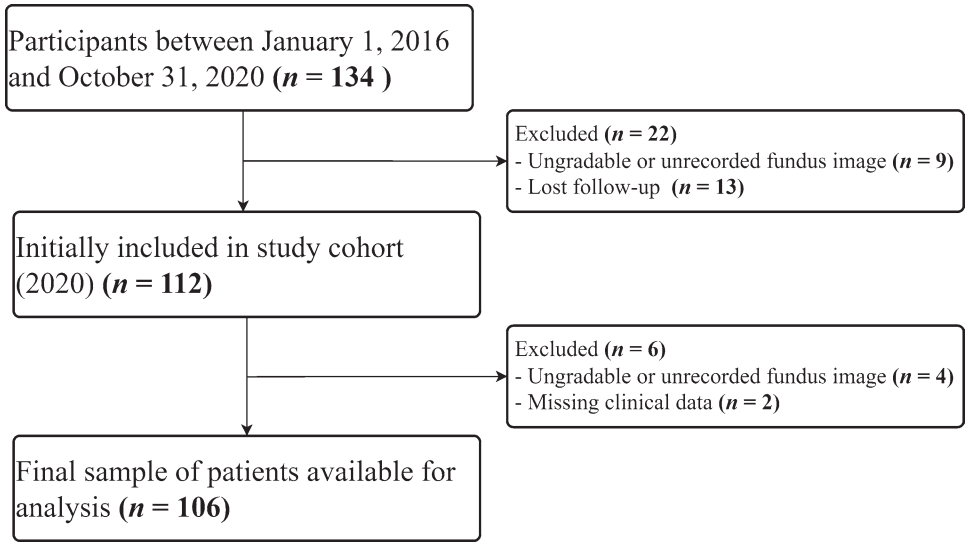

Figure 1. Flowchart of the selected patients.

Table 1

Demographic information of patients with diabetic macular edema undergoing cataract surgery.

	Total		Study group		Control		
	N = 106	%	N = 17	%	N = 89	%	*P* value
Age (mean ± SD)	68.76 ± 9.09		69.59 ± 7.54		68.61 ± 9.38		.685
Gender (%)							.221
Male	48	45.28	10	58.82	38	42.70	
Female	58	54.72	7	41.18	51	57.30	
HbA1C (mean ± SD)	7.20 ± 1.24		7.19 ± 1.57		7.20 ± 1.18		.975
DR status (%)							<.001*
NDR	48	45.28	0	0.00	48	53.93	
Mild NPDR	19	17.92	7	41.18	12	13.48	
Moderate NPDR	20	18.87	4	23.53	16	17.98	
PDR	19	17.92	6	35.29	13	14.61	
Treatment naïve (%)							.006*
0	26	24.53	9	52.94	17	19.10	
1	80	75.47	8	47.06	72	80.90	
Previous IVI of anti-VEGF (%)							.200
No	96	90.57	14	82.35	82	92.13	
Yes	10	9.43	3	17.65	7	7.87	
PRP (%)							.045*
No	84	79.25	10	58.82	74	83.15	
Yes	22	20.75	7	41.18	15	16.85	
IOP (mean ± SD)	14.50 ± 3.63		15.66 ± 4.24		14.28 ± 3.48		.150
IOP-lowering medication (%)							.145
No	77	72.64	15	88.24	62	69.66	
Yes	29	27.36	2	11.76	27	30.34	
CST (baseline)	340.50 ± 46.17		341.20 ± 40.69		339.80 ± 24.63		.573
CST (net change)	18.08 ± 35.65		15.24 ± 45.07		18.62 ± 33.84		.772
Log MAR VA (baseline)	0.50 ± 0.32		0.50 ± 0.30		0.50 ± 0.32		.952
Log MAR VA (net change)	−0.35 ± 0.30		−0.27 ± 0.29		−0.37 ± 0.31		.215

CST = central subfield thickness, DR = diabetic retinopathy, HbA1C = glycated hemoglobin, IOP = intraocular pressure, IVI = intravitreal injection, NDR = no diabetic retinopathy, NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, PRP = pan-retinal photocoagulation, SD = standard deviation, VA = visual acuity, VEGF = vascular endothelial growth factor.
*P value < .05.

P = .952), net change in CST (15.24 ± 45.07 μm vs 18.62 ± 33.84 μm, P = .772), and log MAR VA (–0.27 ± 0.29 vs –0.37 ± 0.31, P = .215) between the 2 groups.

Table 2 details the factors that significantly influenced the net change in CST and log MAR VA in multiple linear regression analysis. Gender (net change in CST: β = –6.047, P = .390; net change in log MAR VA: β = 0.004, P = .904), HbA1c level (net change in CST: β = –2.845, P = .367; net change in log MAR VA: β = –0.008, P = .558), aflibercept IVI during cataract surgery (net change in CST: β = 14.440, P = .369; net change in log MAR VA: β = 0.051, P = .486), and baseline CST (net change in CST: β = –0.241, P = .057; net change in log MAR VA: β < 0.001, P = .808) did not interfere with the morphological and functional outcomes of DME in cataract surgery. Older age was significantly and independently associated with a greater net change in log MAR VA (β = 0.004, P = .037). PDR was significantly and independently associated with a greater net change in CST (β = 52.728, P = .004) and log MAR VA

Table 2

Multiple linear regression analysis for assessing the outcomes of diabetic macular edema.

	CST (net change)			Log MAR VA (net change)		
	β	SE	*P* value	*β*	SE	*P* value
Age	0.063	0.416	.880	0.004	0.002	.037*
Gender						
Female	ref			ref		
Male	–6.047	6.997	.390	0.004	0.032	.904
HbA1c	–2.845	3.141	.367	–0.008	0.014	.558
DR grading						
NDR	ref			ref		
Mild NPDR	7.933	10.770	.463	–0.031	0.049	.525
Moderate NPDR	17.006	10.668	.114	–0.078	0.048	.110
PDR	52.728	17.930	.004*	0.165	0.081	.045*
Treatment naïve						
0	ref			ref		
1	25.669	14.696	.084	–0.045	0.067	.498
IVI of aflibercept						
No	ref			ref		
Yes	14.440	15.981	.369	0.051	0.072	.486
CST (baseline)	–0.241	0.125	.057	<0.001	0.001	.808
Log MAR VA (baseline)	–16.654	11.113	.137	–0.800	0.050	<.001*

CST = central subfield thickness, DR = diabetic retinopathy, HbA1C = glycated hemoglobin, IVI = intravitreal injection, NDR = no diabetic retinopathy, NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, ref = reference, SE = standard error, VA = visual acuity.

*P value < .05.

($\beta = 0.165$, $P = 0.045$). A greater baseline log MAR VA was significantly and independently associated with lower net change in log MAR VA ($\beta = -0.8$, $P < .001$).

4. Discussion

The association between cataract surgery and DME has been widely investigated in previous studies. Inflammation occurring after cataract surgery results in edema or worsening of the preexisting edema in patients with DR.[20,21] Kim et al reported that approximately 22% of patients with diabetes who underwent cataract surgery developed macular edema.[22] As reported previously, the predictors of poor outcomes of DME following cataract surgery in patients with diabetes include early DME; hypertension; and the aqueous levels of VEGF, interleukin-6, and proteins.[23,24] The most severe aspect of DME is attributed to 2 parameters. First, the disruption of retinal tissue caused by retinal edema is not reversible. Although retinal edema subsides after treatment, the atrophied or damaged retinal tissue cannot be regenerated and can cause permanent visual loss.[25] Sun et al further noticed that inner retinal disorganization is a key point to predict VA in CME.[26] Second, the recurrence rate in patients with DME is higher than that in patients without DME, owing to disrupted BRB.[27]

Different methods have been evaluated to control DME progression in patients with diabetes undergoing cataract surgery. As proinflammatory cytokine and VEGF levels increase in the aqueous humor of patients with diabetes undergoing cataract surgery, anti-inflammatory agents and anti-VEGF should be well considered.[28–30] Several studies have shown that topical NSAIDs reduce the odds of developing DME compared with topical corticosteroids and should be considered in patients with diabetes undergoing cataract surgery.[31,32] Studies regarding anti-VEGF IVI on DME vary among different studies. Fard et al showed that mean CST increased after 1 month in patients with DME who underwent cataract surgery but not in patients treated with bevacizumab. However, the difference was no longer relevant at 6 months.[33] Takamura et al[34] showed that bevacizumab IVI may not only prevent the increase in CST but also reduce the CST of eyes with DME after cataract surgery. Chen et al[35] suggested that cataract surgery with bevacizumab IVI reduces CST and improves VA for cataract and DME in diabetics. Chae et al[36] reported similar results of combined cataract surgery and ranibizumab IVI in DME compared to our study (log MAR VA improved by –0.26 ± 0.24 and CST increased by 23 ± 33 μm at 3 months). Chiema et al[37] also showed that postoperative CST and VA were not statistically significant in patients who underwent cataract surgery and received bevacizumab IVI compared to cataract surgery alone, as the same in our study.

As a primary finding, this study revealed that in patients with DME, aflibercept IVI administered during cataract surgery was not associated with a significant net change in CST and VA at 3 months compared with only cataract surgery. It suggested that the improvement in VA was mainly due to cataract removal. The different DME outcomes in previous studies may be attributed to the half-life of different anti-VEGF agents used in the present study. Reportedly, the vitreous half-life of aflibercept in rabbits is 3.63 days.[38] Till now, no study has assessed the half-life of aflibercept in the human eye. On the contrary, the aqueous half-life of bevacizumab and ranibizumab is 9.82 and 7.19 days, respectively.[39,40] The different half-life of anti-VEGF agents may contribute to differences in cases of VEGF surge, as in cataract surgery.

The effect of aflibercept IVI on cataract surgery staging varied greatly with baseline DR grading. Compared with patients who had the milder form of DR, those with PDR at baseline had had a greater decrease in CST but less VA improvement. The visual prognosis of PDR may differ from other stages of DR owing to the abnormal BRB and choroidal morphology changes. Normally, retinal blood vascular endothelium is composed of tight junctions and could serve as the inner BRB, which prevents the leakage of serum and fluids into the retinal tissue.[41] In patients with the more severe form of DR such as PDR, several molecular mechanisms, including the kallikrein-kinin system, VEGF, inflammation, and pericyte dropout could lead to BRB breakdown.[42] In addition, the thickness of the subfoveal choroid as well as of the subfoveal medium choroidal vessel layer and choriocapillaris layer was significantly reduced.[43] This may explain the poorer prognosis of DME observed in patients with PDR despite a greater CST decrease.

Our method still features several limitations. In Taiwan health insurance regulations, patients who received anti-VEGF IVI should be limited to HbA1c < 10% (mmol/mol); thus, patients who had poorer DM control were not included.

Chou et al reported that the HbA1c level in patients with DME was positively correlated with CST.[44] This may explain why the change in CST and VA was not significantly different. In addition, a relatively lower number of cases may affect the significance level of CST. A large number of cases may help support the significance level in CST and VA. Second, although we excluded patients with observable, structural retinal disorders, such as epiretinal membrane and tractional maculopathy, detecting concurrent macular disease during DME is difficult and may lead to misinterpretation of retinal thickness. Further studies with a longer follow-up and a larger sample size are needed to confirm our results.

5. Conclusions

Simultaneous aflibercept IVI for treating DME may not interfere with the functional and tomographic parameters of cataract surgery relative to cataract surgery alone. Factors influencing the outcomes of patients with DME undergoing cataract surgery are as follows: age, baseline DR staging, and baseline VA. Identifying these factors of DME preoperatively may be an important consideration in preventing it from progressing and for improving the overall visual prognosis.

Author contributions

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