• Clinical Research •

Phacoemulsification surgery in patients with diabetic macular edema: should intravitreal anti-VEGF therapy be performed before or simultaneously with surgery?

Yusuf Ziya Güven[1], Mehmed Uğur Işık[2], Serdar Ilgüy[2], Zübeyir Yozgat[2]

[1]Department of Ophthalmology, Izmir Katip Çelebi University Atatürk Educating and Research Hospital, Izmir 35200, Türkiye
[2]Kastamonu University Kastamonu Training and Research Hospital, Kastamonu 37200, Türkiye
Correspondence to: Yusuf Ziya Güven. Department of Ophthalmology, Izmir Katip Çelebi University Atatürk Educating and Research Hospital, Izmir 35200, Türkiye. yusufziya777@gmail.com
Received: 2024-08-05 Accepted: 2024-12-24

Abstract

● **AIM:** To investigate the optimal anti-vascular endothelial growth factor (VEGF) treatment time in patients with diabetic macular edema (DME) scheduled for cataract surgery.

● **METHODS:** The study was designed to include 4 groups. Twenty-six eyes of 26 patients with diabetes but no retinopathy (DR; group 1), 17 eyes of 17 patients with DR but no DME (group 2), and 19 eyes of 19 patients with DME who received anti-VEGF therapy concurrently with cataract surgery (group 3), and 21 eyes of 21 patients who received anti-VEGF therapy for DME 1wk before cataract surgery (group 4). The patients' best corrected visual acuity, intraocular pressure, central and mean macular thickness (CMT and MMT) values were noted on the day of surgery, postoperative day 1, week 1, and month 1.

● **RESULTS:** There was a significant increase of CMT after cataract surgery in groups 1, 2, and 3 (P<0.001, P=0.044, and P=0.034, respectively) but not in group 4 (P=0.948). The change in MMT was the same as CMT (P=0.009, P=0.006, P=0.011, and P=0.172, respectively). There was a higher increase in CMT and MMT in group 2 compared to group 1 at the 1st month after surgery (P=0.002 and P=0.001, respectively).

● **CONCLUSION:** In eyes with DME undergoing cataract surgery, preoperative anti-VEGF treatment may be more effective than simultaneous intravitreal anti-VEGF with surgery.

● **KEYWORDS:** cataract surgery; diabetic macular edema; timing of anti-vascular endothelial growth factor therapy

DOI:10.18240/ijo.2025.04.09

Citation: Güven YZ, Işik MU, Ilgüy S, Yozgat Z. Phacoemulsification surgery in patients with diabetic macular edema: should intravitreal anti-VEGF therapy be performed before or simultaneously with surgery? *Int J Ophthalmol* 2025;18(4):637-641

INTRODUCTION

Diabetes mellitus (DM) is a problem that is becoming increasingly common across the globe[1]. It is also inevitable diabetic ocular complications will increase. Diabetic macular edema (DME) and cataract are the main causes of vision loss in diabetic patients. DM patients are 2-5 times more predisposed to cataract formation compared to the population as a whole[2]. DM can cause both onset of cataracts and progression of existing cataracts. Although the treatment of cataract is simple and straightforward, postoperative process is more challenging in diabetic patients because macular edema and diabetic retinopathy (DR) may begin or worsen as a result of cataract surgery. Pseudophakic macular edema (PME) and progression of DME are the two causes of macular edema, which leads to decrease vision after cataract surgery in diabetic patients.

PME, which can develop even after uneventful cataract surgery, has been facilitated and increased, especially after the use of optical coherence tomography (OCT) widely. Although the pathophysiology of PME is unclear it may occur as a result of an inflammatory response to surgical trauma[2]. As a result of surgical trauma, the secretion of proinflammatory cytokines and vascular endothelial growth factor (VEGF) increases, the blood retinal barrier is damaged, and macular edema develops[2-3]. Inflammation-based comorbidities such as uveitis and diabetes increase the risk of PME[4-5].

DME is the most common cause of vision loss in DR[6] and is often recurrent, making it more difficult to treatment than cataracts. Rising ischemia, oxidative stress and inflammation in DM increase the release of VEGF and proinflammatory cytokines, which disrupt blood retina barrier, increased vascular permeability and result in DME[2]. As mentioned,

proinflammatory cytokines and VEGF play a role in both DME and PME. Patients with prior treatment for DME or who have had cataract surgery in the presence of DME have an increased risk of macular edema progression[7].

Since DME and PME have similar causes and treatments, there is no need for a differential diagnosis. Pre-operative topical nonsteroidal anti-inflammatory drugs (NSAIDs), post-operation intravitreal anti-VEGFs and dexamethasone implant treatments are used in the treatment[2]. In particular, there is no clear consensus on the timing of intravitreal treatments.

Our aim is both to examine the impact of pre-operative DR presence on post-operative macular edema in patients with DME, scheculed for cataract surgery and to determine the optimal timing of anti-VEGF therapy.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective, observational study was conducted in accordance with the principles of the Declaration of Helsinki. The local ethics committee approval was taken (2023-0011). Informed consent was waived due to the retrospective nature of the study.

Participants Patients that underwent phacoemulsification surgery with posterior chamber intraocular lens implantation without complication (such as posterior capsule rupture, vitreous loss, and *etc*.) were included in the study. This study was composed of four groups as follows: group 1, 26 eyes of 26 patients with diabetes but no DR; group 2, 17 patients of 17 patients with DR but no DME; group 3: 19 patients with DME who was applied intravitreal anti-VEGF (aflibercept) therapy combined with phacoemulsification surgery; group 4: 21 patients with DME who was applied intravitreal anti-VEGF (aflibercept) therapy 1wk before the phacoemulsification surgery.

Methods Intravitreal injections are planned according to the treat and extend regimen in our clinic. Three doses of aflibercept loading were completed for each of the patients included in groups 3 and 4, and then, when deemed necessary, injection intervals were extended. Then, the surgeries were performed when after the extension protocol has started (at least after 4 injections). During the COVID-19 pandemic, patients who were planned to undergo elective surgery, such as cataract surgery, were unable to enter the operating room before the polymerase chain reaction (PCR) test negativity was confirmed. Therefore, since we could not verify the COVID-19 PCR negativity on the control day for some patients with DME, who had intravitreal anti-VEGF injection and needed cataract surgery, we requested PCR confirmation after intravitreal injection for these patients. Afterwards, cataract surgery was planned as soon as possible (usually after 1wk) in order not to be the test invalidity for the patients who were PCR negative. Group 4 in our study was formed with these patients.

The patients were evaluated with a complete ophthalmological examination on the preoperative, postoperative 1st day, 7th day and 28th day. Best corrected visual acuity (BCVA), non-contact pneumatic tonometry, slit lamp biomicroscopy, dilated fundus examination, and spectral domain optical coherence tomography (SD-OCT; Zeiss Cirrus HD OCT 5000) were performed in all visits. Mean macular thickness (MMT) and central macular thickness (CMT) were noted using automated data obtained from the OCT device. We have noted the effective phacoemulsification time (EFX) values of the each cataract surgery. Also, in addition to proliferative DR, patients with other retinal diseases, including glaucoma, age-related macular degeneration, retinal vein occlusion, neurodegenerative disease, and a history of uveitis, were not included in the study. In addition, eyes with refractive errors of more than ±6 diopters (in spherical equivalent), those who have undergone any intraocular surgery previously, previously applied intravitreal dexamethasone implant, previously undergone retinal laser photocoagulation, and low-quality OCT images in which retinal features could not be identified at any control visit were not enrolled.

Statistical Analysis Analysis were performed using the SPSS statistical software for Windows, version 26 (IBM, Armonk, NY, USA). The descriptive statistics are expressed as means±standard deviations for variables with normal distributions, medians (interquartile range for non-normal distributions), and the number of cases and percentages (%) for nominal variables. The Kolmogorov-Smirnov distribution test was used to examine the normal distribution. Pearson Chi-square test and Fisher's Exact test were used for comparison of descriptive statistics, as well as qualitative data. When comparing quantifiable data between two groups, the Mann-Whitney *U* test was used when the data did not follow a normal distribution, while the Student's *t*-test was used when the data did follow a normal distribution. Non-normally distributed quantifiable data were compared using the Kruskal-Wallis test for more than two groups, and the group responsible for the difference was investigated using the Mann-Whitney *U* test. When comparing three or more sets of quantifiable data with a normal distribution, an ANOVA test was employed, and the group responsible for the difference was identified using the post hoc Tukey test. As for parametrically distributed data, the repeated measurement analysis test was used to compare the changes in two groups across multiple control times, while in the case of non-parametrically distributed data, the Mann-Whitney *U* test was applied by calculating the difference between the two control times in the groups independently in order to investigate the difference between the two groups in the change at various control times. Results were analyzed

Table 1 Demographic and ocular parameters of patients

Parameters	Group 1 (*n*=26)	Group 2 (*n*=17)	Group 3 (*n*=19)	Group 4 (*n*=21)	*P*
Gender (female/male)	12/14	6/11	8/11	8/13	0.897
Age (y)	66.8±7.5	64.0±8.8	63.6±8.1	68.2±8.0	0.218
DM duration (y)	15.4±4.5	15.6±3.8	15.8±5.4	15.3±5.9	0.988
HbA1c (%)	8.7±2.2	8.2±2.5	8.3±1.9	9.3±2.1	0.555
IOP (mm Hg)	13.9±2.1	14.0±2.0	14.3±2.0	13.8±2.0	0.886
Preop. BCVA (logMAR)	0.73±0.31	0.83±0.51	0.96±0.46	0.92±0.44	0.308
Postop. 1mo BCVA (logMAR)	0.01±0.04	0.19±0.36	0.47±0.39	0.53±0.48	0.0001
EFX (s)	12.3±4.9	15.6±10.6	16.0±9.0	20.1±12.0	0.643

DM: Diabetes mellitus; IOP: Intraocular pressure; BCVA: Best corrected visual acuity; EFX: Effective phacoemulsification time.

Table 2 Comparison of the macular thickness measurements mean±SD/median (IQR)

Parameters	Group 1	Group 2	P^c	Group 3	Group 4	P^d
MMT						
Preop.	282.3±17.8/277 (273, 300)	282.5±21.5/285 (268, 301)	0.979	303.5±77.9/283 (259, 306)	299.1±39.3/330 (321, 357)	0.367
Postop. 1d	279.9±15.8/274 (270, 296)	284.5±19.0/295 (278,306)	0.522	307.0±72.7/289 (270,304)	325.6±72.6/359 (326,413)	0.373
Postop. 1wk	283.4±14.1/279 (273,299)	293.4±23.0/311 (291,316)	0.124	303.6±67.4/291 (270, 308)	314.8±48.4/361 (318, 406)	0.116
Postop. 1mo	287.7±16.4/280 (278, 302)	299.0±35.5/320 (307, 336)	0.204	315.0±69.3/291 (272, 320)	324.1±51.9/392 (333, 400)	0.343
P	0.009[a]	0.006[a]		0.011[b]	0.172[b]	
CMT						
Preop.	254.7±23.7/247 (223, 281)	243.5±43.0/229 (215, 244)	0.298	288.4±125.4/255 (222, 317)	286.0±77.7/314 (264, 456)	0.390
Postop. 1d	253.4±30.8/247 (223, 282)	240.3±16.8/241 (219, 250)	0.199	286.8±120.6/253 (208, 316)	283.4±81.8/311 (268, 398)	0.552
Postop. 1wk	255.0±23.2/250 (228, 279)	254.7±38.8/240 (238, 252)	0.979	285.6±115.1/258 (221, 324)	284.0±76.6/313 (267, 421)	0.683
Postop. 1mo	263.6±26.5/262 (232, 290)	271.4±52.4/268 (246, 292)	0.529	294.7±116.3/262 (221, 327)	323.3±106.2/361 (278, 389)	0.411
P	0.001[a]	0.044[a]		0.034[b]	0.948[b]	

MMT: Mean macular thickness; CMT: Central macular thickness. [a]Repeated measurement analysis, [b]Kruskal Wallis. [c]*P*: Group 1 *vs* Group 2; [d]*P*: Group 3 *vs* Group 4.

using a 95% confidence interval (CI) and $P<0.05$ was considered statistical significance.

RESULTS

There were no significant difference in sex, age, duration of DM and HbA1c between all groups (Table 1). The EFX values used during surgery was 12.3±4.9s in group 1 and 15.6±10.6s in group 2. Groups 1 and 2 were similar in terms of EFX used in surgery (P=0.892). The EFX used during surgery was 16.0±9.0s in group 3 and 20.1±12.0s in group 4. Groups 3 and 4 were similar in terms of EFX used in surgery (P=0.472). When the comparison was made among the 4 groups, there was no significant difference in terms of EFX values (P=0.643; Table 1).

Baseline BCVA was similar between the 4 groups (P=0.308). Post-operative BCVA at 1st month was better in groups 1 and 2 compared to groups 3 and 4 (P=0.0001). There was no significant difference between groups 1and 2 and groups 3 and 4 in terms of BCVA change (P=0.378, P=0.999 respectively).

Groups 1 and 2 were similar in all followup timepoints in terms of MMT and CMT values (Table 2). Groups 3 and 4 were also similar in terms of MMT and CMT values in all timepoints (Table 2). There were significant increases in MMT and CMT values in groups 1, 2, and 3 (Table 2). Although there was an increase in MMT and CMT values in group 4, these increases were not significant (Table 2).

When the difference (delta values) in CMT and MMT changes of groups 1 and 2 were analyzed by repeated measurement analysis, there was a higher increase in CMT and MMT values in group 2 in the 1st month compared to group 1 (P=0.002 and P=0.001, respectively, repeated measurement analysis). When the difference in CMT and MMT changes of group 3 and 4 were analyzed, the increaments of the MMT and CMT values in group 4 compared to group 3 were similar at 1st month (P=0.506 and P=0.817, respectively, Mann-Whitney U test).

DISCUSSION

These results suggested that DM patients with DR may be at greater risk for macular edema, although they do not negatively affect visual outcomes after phacoemulsification. Surgical trauma can disrupt the blood retinal barrier, leading to increased secretion of proinflammatory cytokines and VEGF, which are involved in the pathogenesis of PME[2]. Also, inflammation and VEGF are triggered by ischemia or hypoxia in DR[8-9]. Moreover, Patel *et al*[10] demonstrated that VEGF in an aqueous sample obtained from patients with

DR who underwent cataract surgery increased 10 fold more than baseline values at postoperative 1st day and decreased to normal levels at 1st month after surgery. Considering the role of increased inflammation and VEGF's role in both DR and PME pathogenesis[11], PME may be more likely to occur in DR patients undergoing cataract surgery compared DM patients without DR. Although there is no prominent macular edema in patients with DR after cataract surgery, the increase in macular thickness may be more triggered by the effect of preexisting and more increased VEGF and inflammation compared DM patients without DR. Some studies demonstrated improved CMT and BCVA values at the end of the first month when anti-VEGF was used at the end of routine cataract surgery in cases presenting with DR without edema compared to control groups[12-13]. We think that prophylactic anti-VEGF therapy before cataract surgery may take into account even in the absence of significant macular edema in DR patients.

Macular edema management in patients with coexisting DME will undergo cataract surgery is still controversial. Cataract surgery may exacerbate coexisting DME because of increased inflammatuar cytokines and VEGF[7,14]. Also, pre-existing DME is one of the main risk factors for progression of macular edema after uneventful cataract surgery in DM patients[2,15]. Thus, peroperative or combined anti-VEGF therapy is becoming more common in patients with DME who will undergo cataract surgery. Lanzagorta-Aresti *et al*[15] compared cataract surgery without anti-VEGF and anti-VEGF combined cataract surgery in DME patients and observed that the anti-VEGF combined group had better in both BCVA and CMT outcomes, whereas CMT was also minimally increased up to 3mo even in the anti-VEGF group. On the other hand, Salehi *et al*[16] showed that there was no significant difference the CMT and BCVA values at 6th month between patients who received anti-VEGF simultaneously with cataract surgery and those without. However, the authors argued that combined anti-VEGF therapy with cataract surgery prevented the progression of maculopathy and retinopathy. de Carlo *et al*[17] demonstrated that capillary flow was very reduced in cystoid edema areas in patients with DME in OCT angiography, and the flow was observed again after anti-VEGF treatment. Preoperative or simultaneous anti-VEGF can be applied to DME patients who will undergo cataract surgery, as the mechanical compression effect of cystoid form edema of PME and DME may further impair the already damaged retinal perfusion in diabetic patients. We think that peroperative anti-VEGFs may contribute to the macular anatomy by reducing increased vascular permeability and angiogenic mediators in DME patients undergoing cataract surgery, at least in the short term. We often neglect the treatment of DME and possible PME during cataract surgery, this is maybe a more important problem than we think, because the prolongation of the edema period and increasing macular edema may cause functional healing more difficult.

Although we have treatment options such as anti-VEGF in our patients who will undergo cataract surgery with DME, the optimization of the treatment timing has not been clearly demonstrated. We applied simultaneously with the surgery (group 3) and anti-VEGF treatment one week before the surgery (group 4). In our study, there was no statistical difference in MMT, CMT and the final BCVA all control times between group 3 and 4. There were significant increases in MMT and CMT values in group 3 whereas these increases were not significant in group 4. In various Meta-analyses and studies, it was shown that better CMT, MMT and BCVA values were obtained in patients who underwent anti-VEGF simultaneously with cataract surgery compared to patients who had only cataract surgery[15,18-19]. On the other hand, Yumuşak and Örnek[20] performed ranibizumab 2wk before, intraoperatively, and 2wk later, to patients with DME who will undergo cataract surgery. The authors observed that foveal thickness increased in all 3 groups at 3th month, but a decrease in foveal thickness was observed after the 1st month in the applied preoperative ranibizumab group, while a continuous increase in the other groups. In another study, one of the 2 groups receiving single dose of ranibizumab per month for 3mo, underwent cataract surgery with the last dose of anti-VEGF, while the other group received cataract surgery with the first dose of anti-VEGF[21]. It was observed that BCVA was better and CMT was lower in the group in which preoperative ranibizumab was started. We found CMT increased in both groups, but we applied one dose of anti-VEGF, while 3 doses were applied in the mentioned study.

The preoperative or simultaneous regimen decision in patients with DME who will undergo cataract surgery can also be evaluated based on the clearance of anti-VEGF. Anti-VEGFs are cleared by passing to the posterior chamber rather than local metabolism in the retina[22]. It is known that aqueous humor outflow increases after cataract surgery[23-24]. An intact anterior capsule has also been shown to slow drug clearance from the vitreous[25]. Similarly, after cataract surgery, the transition of anti-VEGF from the posterior chamber to the anterior chamber may increase, that is, its clearance may be accelerated[26]. The clearance of intravitreal anti-VEGFs has been demonstrated to increase following cataract surgery as well as vitrectomy[27]. When these results projected to the current study, clearance of the anti-VEGF agent and transit into the anterior chamber may be slower during the 1wk preoperatively than after the surgery. Thus, anti-VEGF activity in group 4 (anti-VEGF administered 1wk before surgery) may be higher than in group 3, even if it was administered at the

same dose. Based on these approaches, consistent with our results, preoperative anti-VEGF therapy may be more effective than anti-VEGF simultaneously administered with cataract surgery.

In conclusion, in eyes with DME undergoing cataract surgery, preoperative intravitreal anti-VEGF injection may be more effective than simultaneous intravitreal anti-VEGF injection with surgery for limiting the increase in DME. Also, DM patients with DR may have a more pronounced increase in VEGF and inflammation and a tendency to macular edema after cataract surgery than DM patients without DR, so DM patients undergoing cataract surgery may be better monitoring closely in the presence of DR.

ACKNOWLEDGEMENTS

Authors' contributions: Writing original draft Güven YZ; Conceptuzualtion Işık MU; Analyzing data Güven YZ and Işık MU; Collecting data Ilgüy S; Checking spelling and language of manuscript Yozgat Z.

Conflicts of Interest: Güven YZ, None; **Işik MU,** None; **Ilgüy S,** None; **Yozgat Z,** None.

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