• Clinical Research •

Long-term outcomes of anti-VEGF therapy during cataract surgery in eyes with diabetic macular edema: a five-year retrospective cohort study

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Abstract

● **AIM:** To evaluate the long-term outcomes of anti-vascular endothelial growth factor (VEGF) therapy during cataract surgery in eyes with diabetic macular edema (DME).

● **METHODS:** This was a retrospective clinical study. Patients with DME scheduled for cataract surgery were included. Prior to surgery, DME was considered adequately controlled, defined as a central subfield thickness (CST) of ≤300 μm without evidence of significant intraretinal or subretinal fluid on optical coherence tomography. Participants were divided into two groups: 18 patients underwent cataract surgery alone, and 10 received both cataract surgery and anti-VEGF therapy concurrently. The study compared the timing of the initial postoperative anti-VEGF injection and the frequency of injections over 5y. Postoperative outcomes, particularly improvements in best-corrected visual acuity (BCVA) and changes in CST, were also examined.

● **RESULTS:** A total of 28 patients were enrolled, with 10 patients undergoing combined cataract surgery and anti-VEGF therapy (3 males, 62.8±4.4y), while 18 patients (7 males, 70.0±13.6y) underwent cataract surgery alone. The combined therapy group had a significantly longer interval before the initial postoperative anti-VEGF injection (12.2±5.7wk) compared to the cataract-only group (4.4±1.6wk). The combined therapy group also required significantly fewer total anti-VEGF injections over 1, 3, and 5y, with the most notable difference in the first year. There was significant improvement in BCVA from pre- to postoperative stages across all eyes. However, there was no statistically significant difference in postoperative BCVA and CST between the groups.

● **CONCLUSION:** Concurrent anti-VEGF therapy during cataract surgery is associated with lower early postoperative DME recurrence and a longer interval to the first postoperative anti-VEGF injection. This combined approach may reduce early treatment burden.

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

Long-term management of diabetic macular edema (DME) presents a challenge due to the need for regular visits and treatments, often affecting patients' adherence to therapy[1-3]. While fixed-interval regimens of intravitreal anti-vascular endothelial growth factor (VEGF) inhibitors have shown promising outcomes in clinical trials, replicating these results in routine clinical care remains elusive, partly due to the demanding visit schedules[4-6]. Anti-VEGF therapy has become the standard of care for DME following the results of landmark randomized controlled trials, including DRCR.net Protocol I and T, which demonstrated the superiority of ranibizumab with or without deferred laser compared to laser alone[7-12].

The occurrence of cataracts in diabetic patients complicates the management of DME[13-15]. Cataract surgery, a common procedural intervention to restore vision, can itself provoke changes in ocular anatomy and physiology, potentially exacerbating DME or precipitating its recurrence. This presents a clinical challenge, integrating the management of both conditions to optimize patient outcomes. Recent studies have explored the outcomes of cataract surgery in patients with DME, with a focus on the postoperative recurrence of edema and visual acuity improvement[16-20].

Emerging evidence suggests that combining cataract surgery with anti-VEGF therapy may offer synergistic benefits,

potentially stabilizing or improving the course of DME postoperatively[21]. This retrospective analysis contributes to the ongoing dialogue within the ophthalmologic community by directly comparing the efficacy of cataract surgery alone versus cataract surgery combined with anti-VEGF therapy. By examining visual outcomes and the recurrence of macular edema in a diabetic cohort, this study aims to fill gaps in our understanding and guide clinical practice.

Moreover, the timing and frequency of anti-VEGF injections post-surgery remain critical factors that influence treatment outcomes. Understanding these dynamics can help in strategizing more effective treatment protocols that are tailored to the needs of diabetic patients undergoing cataract surgery. This study also aligns with the growing interest in the long-term management of DME, addressing both immediate postoperative outcomes and longer-term visual prognosis.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol was endorsed by the Ethics Committee of Beijing Friendship Hospital (Approval Number: 2023-P2-112-01). Prior to their participation, all individuals provided written informed consent, adhering to the ethical standards stipulated in the Declaration of Helsinki.

Study Design and Participants A retrospective, comparative cohort study was performed in the Department of Ophthalmology, Beijing Friendship Hospital and included 28 eyes with DME and visually significant cataract from January 2017 to December 2018. Participants were allocated to either combined cataract surgery with intraoperative anti-VEGF therapy or cataract surgery alone through surgeon–patient discussions, considering baseline ocular status (*e.g.*, degree of DME control and retinal status), patient preference, and locally consistent clinical guidelines. Ten eyes received combined therapy and 18 eyes underwent cataract surgery alone.

Inclusion and Exclusion Criteria Eligibility for the study was determined based on a set of inclusion and exclusion criteria. Patients were eligible if they were diagnosed with type 2 diabetes mellitus, had clinically significant cataracts requiring surgical intervention, showed stability in DME with less than a 50 μm change in central subfield thickness (CST) as measured by optical coherence tomography (OCT) in the 2mo prior to surgery, maintained stable glycemic control (fasting plasma glucose <8 mmol/L, 2-hour postprandial glucose <10 mmol/L, and postprandial glucose fluctuation <2.2 mmol/L), and exhibited non-proliferative diabetic retinopathy without progression. Exclusion criteria included untreated proliferative diabetic retinopathy, active intraocular inflammation, a history of elevated intraocular pressure or glaucoma, the presence of macular pucker, prior vitreoretinal surgery, high myopia, and lens dislocation. These criteria were consistently applied to ensure the study cohort was well-defined and homogenous, facilitating an accurate evaluation of treatment outcomes.

Surgical Procedure Cataract extraction *via* phacoemulsification and intraocular lens (IOL) implantation were performed in all patients by a single surgeon using a consistent IOL model. No intraoperative complications occurred. In the combined therapy group, intravitreal ranibizumab (0.5 mg/0.05 mL) was injected at the conclusion of cataract surgery. The cataract-only group underwent phacoemulsification and IOL implantation without intraoperative anti-VEGF therapy. Postoperatively, both cohorts received standard topical prednisolone acetate and levofloxacin four times daily for 1mo, with prednisolone tapered weekly until discontinuation. In both groups, postoperative DME recurrence was treated with intravitreal ranibizumab (0.5 mg/0.05 mL) administered on a *pro re nata* (PRN) basis according to prespecified retreatment criteria; no routine switching to other anti-VEGF agents occurred during the study period. Retreatment criteria for PRN injections were predefined as OCT-based DME recurrence, defined by 1) an increase in CST >5% or >50 μm compared with the preceding visit, and/or 2) new or increased intraretinal or subretinal fluid deemed clinically significant by the treating retina specialist, with or without a concomitant decrease in best-corrected visual acuity (BCVA).

Data Collection Patient assessments were conducted monthly for 1y postoperatively and also preoperatively to establish a baseline. The initial assessment included gathering essential patient information such as gender, age, blood glucose levels, BCVA measured in logarithm of the minimum angle of resolution (logMAR), and baseline CST using Heidelberg Spectralis OCT. Throughout the follow-up period, both BCVA and CST were evaluated monthly. DME recurrence (which triggered PRN retreatment) was defined on OCT as a CST increase >5% or >50 μm compared with the preceding visit and/or new or increased intraretinal or subretinal fluid, which align with thresholds used in recent OCT-based clinical studies and trials (PHOTON DME trial criteria; ADVM-022 registered endpoint NCT04418427)[17-20]. Upon such recurrence, additional anti-VEGF therapy was administered, and the timing was meticulously documented. This monthly monitoring continued for 5y, during which the frequency and total number of anti-VEGF injections were recorded.

Statistical Analysis Statistical analyses were performed using SPSS software (version 29). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and are presented as mean±standard deviation (SD); categorical variables are presented as counts and percentages. For postoperative outcomes (BCVA and CST across multiple time points), repeated-measures analysis of variance (ANOVA) with Bonferroni correction was used to assess within

Table 1 Baseline characteristics of patients mean±SD

Parameters	Cataract surgery+anti-VEGF	Cataract surgery alone	*P*
Patients, *n*	10	18	
Age (y)	62.8±4.4	70.0±13.6	0.138
Female, *n* (%)	7 (70)	11 (61)	0.638
Fasting plasma glucose (mmol/L)	6.5±1.1	7.0±1.6	0.978
2-hour postprandial glucose (mmol/L)	8.8±1.1	8.6±1.3	0.819

VEGF: Vascular endothelial growth factor; SD: Standard deviation.

and between-group differences. Adjusted between-group comparisons were performed using analysis of covariance (ANCOVA) and multivariable regression, including age, sex, baseline BCVA, baseline CST, diabetes duration, diabetic retinopathy severity, and preoperative injection history as covariates; model assumptions (normality of residuals and homoscedasticity) were assessed and considered acceptable for the primary adjusted models. Injection-related outcomes were analyzed using Kaplan-Meier survival analysis for time to first postoperative injection (injection-free interval), defined as the time from the date of cataract surgery (index date) to the first postoperative intravitreal anti-VEGF injection; eyes that did not receive any postoperative injections were censored at the last follow-up visit. Between-group comparisons used the log-rank test. A two-sided $P<0.05$ was considered statistically significant. Follow-up completeness was summarized by reporting the number of eyes with available data at years 1, 3, and 5. Missing visits/data were not imputed; analyses were conducted on an available-case basis (complete-case within each analysis).

RESULTS

Baseline Characteristics A total of 28 patients were enrolled in the study, with 10 patients undergoing combined cataract surgery and anti-VEGF therapy, while 18 patients underwent cataract surgery alone. Table 1 provided a comprehensive overview of the baseline characteristics of the study participants. Statistical analysis revealed no significant differences between the two groups in terms of age, gender distribution, and blood glucose levels, indicating a well-matched cohort for the subsequent evaluations of surgical outcomes. Follow-up completeness for injection-related outcomes was years 1, 3, 5: $n=28$. For functional/anatomical outcomes (BCVA and CST), the number of eyes varied by visit due to available-case follow-up; missing observations were handled using available-case analyses.

Postoperative Outcomes Normality testing using the Kolmogorov-Smirnov test indicated that BCVA and CST values across all time points were generally consistent with a normal distribution. This supported the use of parametric analyses with adjusted *P*-values and reporting of 95% confidence intervals (CIs). The preoperative BCVA was 0.84±0.37 in the combined surgery group and 0.73±0.30 in the cataract alone group. The preoperative CST was 319.7±51.9 μm in the combined surgery group and 323.3±52.0 μm in the cataract-only group. There were no statistically significant differences in preoperative BCVA and CST between the two groups. The postoperative outcomes, assessed at various intervals compared to the preoperative period, are summarized in Table 2. Adjusted analyses using ANCOVA and multivariate regression controlling for age and baseline CST confirmed the robustness of group comparisons. The adjusted mean differences and *P*-values are reported in Table 2, showing consistent results with the unadjusted analyses.

Figure 1 showed the Kaplan-Meier survival analysis for time to first postoperative injection, where the combined therapy group demonstrated a significantly longer injection-free interval (log-rank $P<0.001$). The longitudinal trajectories of BCVA and CST confirming that the combined therapy group maintained more stable BCVA and exhibited smaller CST fluctuations up to year 1 compared with the cataract-only group. In addition, patients in the combined group consistently required fewer injections across the follow-up period. Together, these visualizations provide a clearer representation of the temporal trends and group differences, complementing the tabulated results above.

Visual Acuity Outcomes Postoperatively, both groups exhibited significant improvements in BCVA at 7d, 1, 3, 6mo, and 1y compared to their respective preoperative BCVA. There were no statistically significant differences in BCVA between the two groups at any postoperative time point.

Central Subfield Thickness Outcomes Prior to surgery, it was necessary to ensure that DME was adequately controlled and stable before proceeding with cataract surgery. Postoperatively, there were no statistically significant differences in CST when comparing each group's preoperative and postoperative measurements. Additionally, there were no statistically significant differences in CST between the two groups at any postoperative time point.

Postoperative Anti-VEGF Treatment Notably, a significant difference was observed in the timing and frequency of postoperative anti-VEGF injections. For injection-related outcomes, Kolmogorov-Smirnov testing confirmed approximate normality for these variables. Adjusted mean

Table 2 Comparison of BCVA and CST between groups mean±SD

Parameters	Pre-operation	Post-operation				
		Day 7	Month 1	Month 3	Month 6	Year 1
Cataract surgery+anti-VEGF						
BCVA (logMAR)	0.84±0.37	0.54±0.25	0.47±0.22	0.42±0.17	0.47±0.22	0.42±0.19
[a]*P*	-	0.012	0.009	0.003	0.005	0.020
CST (μm)	319.7±51.9	305.5±118.8	309.4±104.2	355.6±167.7	335.5±90.1	320.9±70.4
[a]*P*	-	0.665	0.708	0.539	0.557	0.965
Cataract surgery alone						
BCVA (logMAR)	0.73±0.30	0.56±0.28	0.44±0.16	0.44±0.15	0.50±0.20	0.45±0.21
[a]*P*	-	0.033	0.005	0.001	0.002	0.021
[b]*P*	0.408	0.889	0.856	0.742	0.701	0.724
Adjusted mean difference (95%CI)	0.02 (-0.11, 0.15)	0.06 (-0.08, 0.20)	0.05 (-0.10, 0.21)	0.07 (-0.12, 0.26)	0.04 (-0.15, 0.23)	0.04 (-0.15, 0.22)
Adjusted [b]*P*	0.743	0.392	0.496	0.462	0.673	0.699
CST (μm)	323.3±52.0	298.6±129.6	297.9±109.8	341.7±180.1	344.2±80.9	340.8±64.2
[a]*P*	-	0.34	0.224	0.68	0.231	0.273
[b]*P*	0.866	0.886	0.796	0.849	0.802	0.472
Adjusted mean difference (95%CI)	18.52 (-26.33, 63.37)	27.45 (-20.36, 75.26)	30.21 (-18.73, 79.15)	28.87 (-20.91, 78.65)	31.12 (-18.04, 80.27)	33.38 (-15.80, 82.55)
Adjusted [b]*P*	0.398	0.244	0.223	0.249	0.210	0.170

VEGF: Vascular endothelial growth factor; CST: Central subfield thickness; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; CI: Confidence interval. [a]Intra-group comparison between preoperative and postoperative conditions, [b]Inter-group comparison at the same time points.

Table 3 Postoperative injection outcomes with adjusted analyses mean±SD

Parameters	Cataract surgery+anti-VEGF	Cataract surgery alone	*P*	Adjusted mean difference (95%CI)	Adjusted *P*
Weeks to first postoperative injection	12.2±5.7	4.4±1.6	<0.001	7.80 (4.19, 11.41)	<0.001
Number of injections in 1y	2.2±1.8	6.1±1.5	<0.001	-3.90 (-5.21, -2.59)	<0.001
Number of injections in 3y	3.4±1.7	7.2±1.8	<0.001	-3.80 (-5.14, -2.46)	<0.001
Number of injections between 1 and 3y	1.2±1.1	1.1±0.8	0.814	0.10 (-0.68, 0.88)	0.81
Number of injections in 5y	4.2±2.0	8.1±1.8	<0.001	-3.90 (-5.39, -2.41)	<0.001
Number of injections between 3 and 5y	0.80±0.60	0.83±0.69	0.902	-0.03 (-0.52, 0.46)	0.90

VEGF: Vascular endothelial growth factor; SD: Standard deviation; CI: Confidence interval.

differences with 95%CI and adjusted *P* values are presented in Table 3. Overall, these findings suggest that intraoperative anti-VEGF combined with cataract surgery may be associated with a longer injection-free interval and fewer postoperative injections, particularly during the first postoperative year.

Systemic Health and Diabetic Retinopathy Throughout the follow-up period, there was no observed aggravation of diabetic retinopathy in either group. Additionally, patient monitoring revealed no significant fluctuations in blood glucose levels or blood pressure, and no systemic complications were reported. This stability underscores the safety of the surgical interventions and the efficacy of perioperative management strategies in maintaining systemic and ocular health in diabetic patients undergoing cataract surgery.

Postoperative Complications Transient IOP elevation ≥25 mm Hg occurred in 2 eyes (20.0%) in the combined therapy group and 3 eyes (17.6%) in the cataract-only group (*P*=0.84). Mild anterior chamber inflammation (flare grade

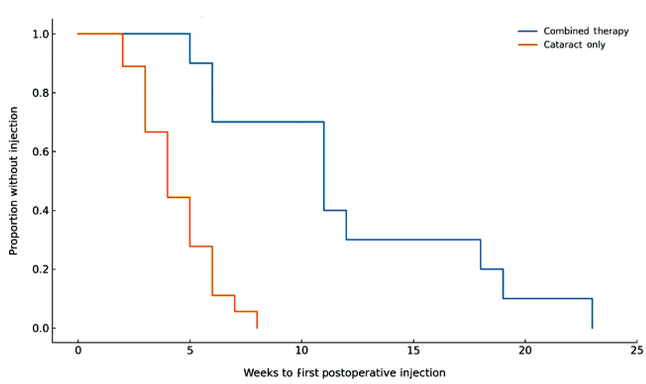

Figure 1 Kaplan-Meier curve depicting the cumulative probability of remaining free from postoperative intravitreal anti-VEGF injection (injection-free interval) in the combined therapy group (cataract surgery+anti-VEGF; *n*=10) versus the cataract-only group (*n*=18) Injection-free interval was defined from the cataract surgery date to the first postoperative injection; eyes without injections were censored at the last follow-up visit. The number at risk decreased over time due to censoring and available follow-up. VEGF: Vascular endothelial growth factor.

≤2+) was observed in 3 eyes (30.0%) and 5 eyes (29.4%), respectively (P=0.96), and resolved within 2wk with topical corticosteroid therapy. No cases of persistent IOL decentration or dislocation and endophthalmitis were noted. No cases of endophthalmitis, retinal detachment, severe intraocular inflammation, or sustained IOP elevation requiring glaucoma surgery were recorded during follow-up. Exploratory analysis revealed no significant association between postoperative IOP elevation or anterior chamber inflammation and subsequent DME recurrence (all P>0.05).

DISCUSSION

This study evaluated the long-term efficacy of combining anti-VEGF therapy with cataract surgery to examine its association with postoperative DME recurrence in a cohort of diabetic patients. The primary findings indicated that the interval before the first postoperative anti-VEGF injection was significantly longer in the combined therapy group compared to the cataract-only group. This extended interval suggested that the concurrent administration of anti-VEGF therapy during cataract surgery might help stabilize the intraocular environment, delaying the need for subsequent interventions. Moreover, the combined therapy group required significantly fewer anti-VEGF injections over the one-year, three-year, and five-year follow-up periods, with the most pronounced reduction observed in the first year. This reduction in injection frequency highlighted the sustained therapeutic effect of the combined treatment, which could translate into lower overall treatment burdens for patients.

Critical Role of VEGF in DME Pathophysiology The pathophysiological role of VEGF in the development of DME is well-documented, with studies indicating a direct correlation between the severity of DME and elevated levels of VEGF within the vitreous. In DME, the pathophysiological role of VEGF is crucial due to its significant contribution to increased vascular permeability and the breakdown of the blood-retinal barrier[22-23]. Elevated VEGF levels in diabetic patients lead to the leakage of fluid into the retinal tissue, resulting in macular edema. Anti-VEGF therapy targets this process by inhibiting VEGF activity, thereby reducing vascular permeability and fluid accumulation, and ultimately improving retinal thickness and visual acuity[24]. Ranibizumab was selected as the anti-VEGF agent for both intraoperative administration in the combined therapy group and postoperative retreatment in both groups, based on local availability, adherence to national clinical practice guidelines, and its well-documented efficacy and safety profile. The applicability of our findings to other anti-VEGF agents such as aflibercept or bevacizumab remains to be established, and direct comparative trials are needed to confirm whether similar long-term benefits can be achieved.

Efficacy of Intraoperative Anti-VEGF Therapy Previous randomized controlled trials have yielded mixed results on the efficacy of intraoperative anti-VEGF therapy. Following cataract surgery, Patel *et al*[25] noted a sharp rise in VEGF levels in the anterior chamber, correlating these spikes with increased risks of DME recurrence. This underpins the rationale for integrating anti-VEGF therapy during cataract surgeries to manage and potentially mitigate postoperative complications[26]. Pastore *et al*[27] described that DME worsening occurred in patients with concurrent DME following cataract surgery. Lanzagorta-Aresti *et al*[28] and Takamura *et al*[29] observed significant improvements in BCVA and reductions in macular thickness, highlighting the benefits of anti-VEGF therapy when combined with cataract surgery. Contrarily, studies by Khodabandeh *et al*[30] and Lim *et al*[31] showed no substantial improvements in visual outcomes, despite some reductions in CST. These discrepancies underscore the complex and variable nature of DME responses to anti-VEGF treatments, suggesting that while some patients benefit significantly, others may not experience marked improvements.

Natural Resolution *vs* Active Intervention Previous research has indicated that cataract surgery may induce both transient worsening and partial spontaneous resolution of DME. Kim *et al*[32] reported that diabetic eyes experienced a 22% incidence of postoperative macular edema, particularly pronounced in those with advanced retinopathy, whereas eyes without retinopathy showed only minimal thickening and substantial visual improvement. Hayashi *et al*[33] similarly observed that DME often worsened during the first 3mo after phacoemulsification, but in approximately one-third of affected eyes, the edema subsequently resolved spontaneously. These findings highlight that cataract surgery itself may alter the natural course of macular thickness in diabetic eyes, with spontaneous resolution occurring in a subset of cases. Our results align with these observations but also demonstrate that adjunctive anti-VEGF therapy is necessary to mitigate recurrence and achieve sustained control of DME. Our approach, therefore, leans towards proactive intervention with anti-VEGF therapy upon the detection of increased retinal edema, rather than awaiting spontaneous resolution, to prevent potential long-term damage.

The integrity of visual acuity is closely linked to the functionality of photoreceptor cells. Early intervention in the treatment of DME was critical to minimize the damage caused by edema to these cells. Prompt treatment helped to reduce retinal swelling and preserve photoreceptor function, thereby enhancing the potential for long-term visual improvement. Delayed treatment, on the other hand, could result in prolonged edema, leading to irreversible damage to the photoreceptors and subsequently poorer visual outcomes[21]. This underscored the importance of early and effective management of DME

to achieve the best possible visual prognosis over the long term. Therefore, the primary objective of our treatment strategy was to minimize the recurrence and duration of DME, thereby preserving retinal cell function and salvaging visual capacity. Cataract surgery, however, could trigger the release of inflammatory factors, potentially leading to the recurrence and exacerbation of DME. Concurrent intraoperative anti-VEGF therapy during cataract surgery may help mitigate early postoperative DME recurrence and worsening. This combined approach not only aided in long-term control of DME but also played a significant role in protecting retinal function and preserving vision.

Operational and Financial Benefits Our findings align with previous research, showing that the time to the first postoperative anti-VEGF injection was extended, and the number of required injections over the first year was significantly reduced in the combined surgery group. This not only delayed the recurrence of DME but also decreased the operational risks and financial burdens associated with multiple injections. The absence of short-term macular edema post-surgery also facilitated better immediate visual outcomes and reduced the risks associated with early postoperative interventions, such as endophthalmitis from injection procedures near the surgical site.

Although postoperative inflammatory responses and IOP fluctuations have been proposed to contribute to DME recurrence, our exploratory analysis did not identify significant associations with CST changes in this cohort. This may reflect the transient and mild nature of these events as well as the limited sample size. Larger studies incorporating standardized inflammatory biomarkers are needed to clarify these relationships.

While our study offered insights into the postoperative dynamics of DME treatment, it was not without limitations. First, the overall sample size was small, and the combined therapy group (n=10) was notably smaller than the cataract-only group (n=18). This imbalance reduces statistical power and increases the risk of type II error, limiting the generalizability of our findings. Moreover, with such a limited cohort, individual outliers—such as patients requiring unusually early or frequent injections—may disproportionately influence group comparisons. Second, the retrospective design introduces inherent limitations, including the potential for incomplete data capture and unmeasured confounding. Allocation of patients was based on physician judgment and patient preference, which may have introduced selection bias. Third, although we performed adjusted analyses (ANCOVA and multivariate regression) controlling for age and baseline CST, other unadjusted covariates may still have influenced outcomes. Fourth, our definition of DME recurrence relied on CST-based thresholds (>5% or >50 μm), which are used in previous studies[34-37] but may not fully reflect qualitative morphological changes. Additionally, our recurrence definition was based solely on quantitative CST thresholds, without incorporating qualitative features such as intraretinal fluid distribution or morphological patterns, which may provide complementary insights. Multimodal imaging should be considered in future studies. Fifth, despite normality testing supporting the use of parametric methods, the modest sample size could affect statistical assumptions, and larger trials would better validate these findings. Finally, the non-randomized, single-center design further limits external validity. Collectively, these limitations underscore the exploratory nature of our findings, and larger, prospective randomized studies are needed to confirm the potential benefit of concurrent anti-VEGF therapy during cataract surgery[38-40].

In conclusion, concurrent anti-VEGF therapy during cataract surgery may provide a potential benefit in managing DME by extending the interval to postoperative retreatment and reducing early treatment burden. This strategy was associated with attenuated early postoperative DME recurrence in our cohort. These findings should be interpreted cautiously given the small sample size and retrospective design, and larger prospective studies are needed to confirm the role of this approach in optimizing outcomes.

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Data Availability Statement: Although these data are not currently publicly available for sharing, requests for sharing can be sent to the corresponding author and will be evaluated on an individual basis.

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