Outcomes of Cataract Surgery in Patients With Exudative Age-related Macular Degeneration and Macular Fluid

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• PURPOSE: To investigate whether having macular fluid on optical coherence tomography (OCT) prior to cataract surgery adversely affected vision or anatomic outcomes after cataract surgery in patients with exudative age-related macular degeneration (AMD).
• DESIGN: Retrospective cohort study.
• METHODS: We examined all patients who underwent cataract surgery and were receiving intravitreal anti–vascular endothelial growth factor (anti-VEGF) injections from January 1, 2012 through December 31, 2016. There were 81 eyes that underwent cataract surgery and had received at least 1 intravitreal anti-VEGF injection for a diagnosis of exudative AMD within 6 months prior to surgery. Data collected included the development of subretinal or intraretinal macular fluid, or subretinal hemorrhage, in the 6 months following surgery; number of injections; best-corrected visual acuity (BCVA); and central subfield thickness (CST).
• RESULTS: There was a significant improvement between preopertive and postoperative BCVA when comparing all patients (P values $<$ .0001) and no significant difference in CST before and after surgery ($P >$ .05). There were 23 eyes with fluid on the preoperative OCT. There were no differences in final BCVA or CST and no difference in the development of fluid postoperatively when compared to patients without fluid preoperatively (all P values $>$ .05). These patients also saw a significant improvement in BCVA (P = .006).
• CONCLUSION: In a real-world setting, patients with both cataracts and wet AMD may safely undergo cataract surgery. Patients with stable preoperative fluid on OCT should be considered for cataract surgery, as these patients did well postoperatively, with no worsening of their neovascular process. (Am J Ophthalmol 2018;192:91–97. © 2018 Elsevier Inc. All rights reserved.)

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TWO OF THE TOP 4 CAUSES OF BLINDNESS IN THE United States are age-related macular degeneration (AMD) and cataracts.[1] As more patients with exudative AMD are being treated with anti–vascular endothelial growth factor (anti-VEGF)[2–5] injections, there are an increasing number of patients that are concomitantly affected by cataracts and are actively receiving anti-VEGF injections. This creates a challenging situation for clinicians who recommend when these patients should undergo cataract surgery. There is concern, though, that inflammation and possibly intraocular pressure fluctuations during cataract surgery may worsen a patient's retinal disease process, especially if that disease is active. Previous studies on this topic have examined patients with stable wet AMD, with a majority either not requiring anti-VEGF therapy[6] or on a stable treat-and-extend regimen.[7] Clinical trials have shown that despite regular and frequent injections, even as part of a clinical trial, many patients still have fluid on OCT. For example, outcomes from the CATT study showed that 70.7% of eyes had any macular fluid at 1 year, 74.5% at 2 years (clinical trial data), and 83.0% at 5 years (real-world follow-up extension study).[4,8,9] The goal of this study was to investigate whether the preoperative presence of macular fluid on OCT in eyes with exudative AMD affects visual outcomes following cataract surgery.

METHODS

THIS STUDY IS IN COMPLIANCE WITH THE HEALTH INSURance Portability and Accountability Act (HIPAA), received prospective Mayo Clinic Institutional Review Board approval, and adhered to the tenets of the Declaration of Helsinki. We performed a retrospective chart review of all patients who underwent cataract extraction and received intravitreal anti-VEGF injections performed at the Mayo Clinic, Rochester, Minnesota campus, from January 1, 2012 through December 31, 2016. Inclusion criteria were a diagnosis of exudative AMD in the operative eye, and that the operative eye had to have had an injection of intravitreal anti-VEGF within the 6-month period prior to surgery; patients had to have at least 6 months of follow-up after cataract surgery. Patients receiving

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ranibizumab 0.5 mg/0.05 mL (Lucentis; Genentech, South San Francisco, California, USA), bevacizumab 1.25 mg/0.05 mL (Genentech, South San Francisco, California, USA), and aflibercept 2 mg/0.05 mL (Eylea; Regeneron, Tarrytown, New York, USA) were included; there was no differentiation between drugs for the purposes of this study. Patients were typically managed using a modified treat-and-extend approach that has been reported previously.[10] Patients were excluded if they were receiving anti-VEGF injections for other diseases such as diabetic macular edema, vein occlusions, or other causes of choroidal neovascularization (CNV). Patients were not excluded if they had other concomitant ocular diseases such as glaucoma or nonproliferative diabetic retinopathy.

We recorded the optical coherence tomography (OCT) findings of the final preoperative OCT and the first 2 OCTs postoperatively. The preoperative OCT was assessed for any evidence of intraretinal or subretinal fluid. We interpreted each postoperative OCT for new or worsening subretinal fluid, intraretinal fluid, or subretinal hemorrhage within 6 months following cataract surgery and recorded the central subfoveal thickness (CST) for each OCT. We also documented the number of intravitreal injections 6 months before and 6 months after cataract surgery, best-corrected visual acuity (BCVA), and the type of anti-VEGF drug used. Visual acuity was recorded using Snellen acuity and converted to logMAR acuity. We recorded the BCVA at the last preoperative visit prior to surgery, at 4-6 weeks following cataract surgery, and then at 6 months postoperatively. Postoperative refractions were performed by certified ophthalmic assistants and BCVA was determined using a projected Snellen acuity chart.

Data were collected and entered into Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). For statistical analysis, we used JMP software version 10.0 (SAS Institute, Cary, North Carolina, USA). For within-group comparisons, a paired *t* test was used; and for comparisons between groups, the Wilcoxon rank sum test was performed. Group comparisons of the categorical data were performed using the Fisher exact test. A *P* value less than .05 was considered to be statistically significant.

RESULTS

A TOTAL OF 131 PATIENTS UNDERWENT CATARACT extraction and also received an ipsilateral intravitreal injection during the 4-year study period. Of these, 81 eyes of 72 patients were included in the study. Eight eyes were excluded for receiving an initial injection at the time of cataract surgery, 5 for receiving intravitreal steroids, and, lastly, 37 eyes were excluded for receiving anti-VEGF injections for either a vein occlusion or diabetic retinopathy.

TABLE 1. Distribution of Visual Acuity of All Eyes (N = 81) Before and After Cataract Surgery

Visual Acuity (Snellen)	Preoperative	4-6 Weeks Postoperative	6 Months Postoperative
>20/40	6 (7.4%)	37 (45.7%)	49 (60.5%)
20/50-20/100	44 (54.35)	32 (39.5%)	25 (30.9%)
<20/100	31 (38.3%)	12 (14.8%)	7 (8.6%)

There were 57 eyes of female patients (70.4%), and the mean age of the patients at the time of cataract surgery was 82.5 ± 6.1 years. Thirty-eight eyes (46.9%) were treated with bevacizumab prior to cataract surgery, 34 (42.0%) with aflibercept, and 9 (11.1%) with ranibizumab. The median time from the last injection to cataract surgery was 13 days (4.5, 24.5; 25th and 75th quartiles, respectively). The mean follow-up period after cataract surgery was 475.9 ± 210.4 days.

Preoperatively, 6 eyes (7.4%) had 20/40 or better best-corrected visual acuity, 44 eyes (54.3%) had vision between 20/50 and 20/100, and 31 eyes (38.3%) had vision worse than 20/100. At 4-6 weeks after cataract surgery, 37 eyes (45.7%) had 20/40 or better BCVA, 32 (39.5%) had vision between 20/50 and 20/100, and only 12 eyes (14.8%) had vision worse than 20/100. At 6 months postoperatively, 49 eyes (60.5%) had 20/40 or better BCVA, 25 (30.9%) had vision between 20/50 and 20/100, and only 7 eyes (8.6%) had vision worse than 20/100 (Table 1). The mean logMAR preoperative BCVA was 0.76 ± 0.48 (Snellen acuity 20/115) and the mean preoperative CST was 277 ± 50 μm. The mean logMAR postoperative BCVA at 4-6 weeks postoperatively was 0.44 ± 0.39 (Snellen acuity 20/55) and at 6 months following surgery the mean logMAR BCVA was 0.35 ± 0.29 (Snellen acuity 20/45), both of which were significantly improved from the preoperative BCVA (*P* values < .0001). The mean postoperative CST measurements were 277 ± 50 μm and 286 ± 83 μm, with no significant difference at either measurement compared to the preoperative CST (*P* = .2730 and *P* = .1605, respectively, Table 2). There was no difference in the mean number of injections in the 6-month period before and after surgery (4.3 ± 1.4 preoperatively, 4.2 ± 1.5 postoperatively, *P* = .6210).

• **ANALYSIS OF PREOPERATIVE FLUID:** When comparing the eyes with preoperative fluid against those without preoperative fluid, there was no difference in preoperative or postoperative BCVA at both 4-6 weeks and 6 months after cataract surgery (Table 3). There was a trend toward better final BCVA in the eyes without fluid preoperatively, but it was not a significant difference (*P* = .1090 at 4-6 weeks and *P* = .06 at 6 months postoperatively, Table 3). There was no significant difference in CST measurements at any time point, in development of new or worsening

TABLE 2. Mean Best-Corrected Visual Acuity and Central Subfoveal Thickness Measurements Before and After Cataract Surgery

	Mean Preop logMAR BCVA (Snellen)	Mean 4- to 6-Week Postop logMAR BCVA (Snellen)	*P* Value	Mean 6-Month Postop logMAR BCVA (Snellen)	*P* Value (Preop to Postop)	Mean Preop CST (μm)	Mean 1st Postop CST (μm)	*P* Value	Mean 2nd Postop CST (μm)	*P* Value (Preop to Postop)
All eyes (n = 81)	0.76 ± 0.48 (20/115)	0.44 ± 0.39 (20/55)	<.0001*	0.35 ± 0.29 (20/45)	<.0001*	277 ± 50	286 ± 83	.27	292 ± 92	.16
Eyes with fluid preoperatively (n = 23)	0.69 ± 0.37 (20/98)	0.47 ± 0.28 (20/59)	.01*	0.44 ± 0.29 (20/55)	.03*	289 ± 52	321 ± 126	.20	336 ± 136	.08
Eyes without fluid preoperatively (n = 58)	0.78 ± 0.46 (20/121)	0.43 ± 0.43 (20/54)	<.0001*	0.31 ± 0.28 (20/41)	<.0001*	272 ± 49	272 ± 51	.76	274 ± 59	.56

BCVA = best-corrected visual acuity; CST = central subfoveal thickness; OCT = optical coherence tomography; Postop = postoperative; Preop = preoperative.
Asterisk (*) indicates significant *P* value.

intraretinal or subretinal fluid, or in the number of injections postoperatively (*P* values > .05, Table 3).

• **POSTOPERATIVE COMPLICATIONS:** After cataract surgery, 2 eyes (2.5%) developed a new subretinal hemorrhage; 1 had a subretinal hemorrhage preoperatively that re-bled 1 week after surgery. Vision in this eye improved from count fingers before cataract surgery to 20/200 at the final follow-up visit. The other patient developed a new subretinal hemorrhage 4 months after cataract surgery and vision declined from 20/60 before cataract surgery to 20/100 at the final follow-up visit. Twenty-five eyes (30.9%) developed new or worsening intraretinal and/or subretinal fluid. There were 12 eyes (14.8%) with new or worsening intraretinal fluid and 16 eyes (19.8%) that developed new or worsening subretinal fluid. One patient developed a posterior capsule rupture intraoperatively during phacoemulsification, requiring an anterior vitrectomy with placement of sulcus intraocular lens. There were 8 patients who developed worse visual acuity at 6 months after cataract surgery. These patients were more likely to have preoperative macular fluid ($P = .03$) and new or worse subretinal fluid following cataract surgery ($P = .04$). There was no difference in the development of new or worsening intraretinal fluid, timing of injections prior to surgery, or any CST measurement (all *P* values > .05). When we compared the patients who developed new or worsening fluid or hemorrhage vs the patients who remained stable throughout the postoperative period, there was no difference in preoperative or postoperative BCVA, CST preoperatively or postoperatively, the days from last injection to cataract surgery, or the presence of fluid preoperatively (all *P* values > .05, Table 4). However, there was a significant difference in the mean change in BCVA from the preoperative visit to the 6-month postoperative visit ($P = .02$), but there was no difference in the BCVA at 6 months ($P = .08$).

DISCUSSION

IN OUR STUDY THERE WAS AN IMPROVEMENT IN THE MEAN BCVA at both 4-6 weeks and 6 months postoperatively in AMD patients actively being treated with intravitreal anti-VEGF injections following cataract surgery. The patients with fluid preoperatively also had a significant improvement in visual acuity following cataract surgery, without a significant worsening of their macular fluid. The results of this study show that patients with actively managed wet AMD, even those with retinal fluid on OCT, may undergo cataract surgery and see a significant improvement in BCVA without a worsening of their underlying neovascular process.

Going back to the 1970s, Blair and Ferguson describe a case series of 6 patients with AMD who underwent cataract

TABLE 3. Comparing Preoperative and Postoperative Parameters in Eyes With Fluid on the Preoperative Optical Coherence Tomography Scan Versus Eyes Without Fluid Preoperatively

	Eyes With Fluid Preoperatively (N = 23)	Eyes Without Fluid Preoperatively (N = 58)	*P* Value
Preoperative logMAR BCVA (Snellen)	0.69 ± 0.37 (20/98)	0.78 ± 0.46 (20/121)	.67
4-6 weeks postoperative logMAR BCVA (Snellen)	0.47 ± 0.28 (20/59)	0.43 ± 0.43 (20/54)	.10
Mean change in logMAR BCVA (Snellen)	0.22 ± 0.34	0.35 ± 0.42	.10
P value	.006*	<.0001*	-
6 months postoperative logMAR BCVA (Snellen)	0.44 ± 0.29 (20/55)	0.31 ± 0.28 (20/41)	.06
Mean change in BCVA (logMAR, preoperative to postoperative)	0.31 ± 0.63	0.46 ± 0.41	.32
P value	.026*	<.0001*	-
Preoperative CST (μm)	289 ± 52	272 ± 49	.15
Postoperative 1st CST (μm)	321 ± 126	272 ± 51	.16
Mean change in CST (μm)	+32 ± 25	-2 ± 4	.31
P value	.20	.76	-
Postoperative 2nd CST (μm)	336 ± 136	274 ± 59	.16
Mean change in CST (μm)	+47 ± 26	-3 ± 4	.52
P value	.08	.56	
Eyes with new IRF	4 (17.4%)	8 (13.8%)	.68[a]
Eyes with new SRF	6 (26.1%)	10 (17.2%)	.37[a]
Eyes with new subretinal hemorrhage	1 (4.3%)	1 (1.7%)	.49[a]
Mean number of injections preoperatively	4.1 ± 1.2	4.4 ± 1.5	.28
Mean number of injections postoperatively	3.8 ± 1.5	4.3 ± 1.5	.09

BCVA = best-corrected visual acuity; CST = central subfoveal thickness; IRF = intraretinal fluid; SRF = subretinal fluid.
Asterisk (*) indicates statistical significance.
[a]Fisher exact test.

surgery. All 6 patients had a worsening of their visual acuity and worsening of their neovascular processes.[11] Since then, several studies have examined the effects of cataract surgery on the progression of wet and dry AMD,[12–20] but none of these studies evaluated patients with neovascular AMD undergoing cataract surgery. With the advent of anti-VEGF injections, more patients with exudative AMD are stabilizing, if not improving, and the visual decline may often be attributable to geographic atrophy progression or to cataract progression. These patients then undergo cataract surgery, which poses a new question: does cataract surgery worsen wet AMD in patients being actively managed? Saraf and associates reported that patients with stable neovascular AMD receiving anti-VEGF injections using a treat-and-extend protocol who underwent cataract surgery had a significant improvement in BCVA ($P = .049$), but did have a significantly higher central retinal thickness ($P = .011$) at 6 months postoperatively as compared to those eyes with late AMD that did not undergo cataract surgery.[7] This study only followed stable patients and excluded complicated cataract surgeries. Still, it indicates that stable patients receiving anti-VEGF injections on a fixed interval for neovascular AMD who then undergo cataract surgery may improve their BCVA without worsening their underlying AMD. Our study included patients with other ocular diseases such as glaucoma and mild diabetic retinopathy, as well as complicated cataract surgeries. We examined patients with preoperative macular fluid prior to cataract surgery and found that these patients also saw a benefit in visual acuity following cataract surgery.

Of the clinical trials evaluating the use of intravitreal anti-VEGF for the treatment of exudative AMD, only the SECURE, HORIZON, and MARINA trials mention cataract surgery in the initial report.[21–23] The SECURE study reports that 6 patients underwent cataract surgery during the trial period, but the report did not discuss outcomes.[22] The ANCHOR trial reported 5 patients who underwent cataract surgery and that there was no difference in visual acuity outcomes compared to the other patients in the same treatment cohorts.[21] The HORIZON study mentions the percentage of patients undergoing cataract surgery in each treatment cohort, but again, no outcomes were reported.[23] In a subsequent analysis of both the MARINA and ANCHOR trials published in 2011 by Rosenfeld and associates,[24] they had 23 eyes in the ranibizumab-treated cohort, 28 fellow eyes of the ranibizumab cohort, and 16 eyes in the non-ranibizumab cohort that underwent cataract surgery. Of the 23 eyes receiving injections, they report a mean improvement in visual acuity of 10.4 letters at 3 months post cataract surgery. In comparing the 3 cohorts there was no difference in

TABLE 4. Comparing Preoperative and Postoperative Parameters in Eyes That Developed Worsening Retinal Fluid Following Cataract Surgery Versus Eyes That Did Not Develop New or Worsening Retinal Fluid

	Eyes With Worsening Retinal Fluid Postoperatively (N=26)	Eyes Without Worsening Retinal Fluid Postoperatively (N=55)	*P* Value
Preoperative logMAR BCVA (Snellen)	0.71 ± 0.41 (20/103)	0.77 ± 0.51 (20/118)	.36
4-6 weeks postoperative logMAR BCVA (Snellen)	0.44 ± 0.33 (20/55)	0.44 ± 0.42 (20/55)	.63
Mean change in logMAR BCVA (Snellen)	0.28 ± 0.40	0.33 ± 0.42	.46
P value	.002*	<.0001*	
6 months postoperative logMAR BCVA (Snellen)	0.44 ± 0.37 (20/55)	0.30 ± 0.22 (20/40)	.08
Mean change in BCVA (logMAR, preoperative to postoperative)	0.23 ± 0.43	0.50 ± 0.49	.02*
P value	.0093*	<.0001*	
Preoperative CST (μm)	277 ± 58	278 ± 46	.80
Postoperative 1st CST (μm)	296 ± 80	283 ± 84	.30
Mean change in CST (μm)	+18 ± 12	+4 ± 10	.16
P value	.15	.66	
Postoperative 2nd CST (μm)	308 ± 117	283 ± 76	.54
Mean change in CST (μm)	+30 ± 20	+4 ± 8	.07
P value	.14	.64	
Eyes with preoperative fluid, n (%)	9 (34.6%)	14 (25.5%)	.40
Mean number of preoperative injections	4.42 ± 1.58	4.25 ± 1.35	.53
Mean number of postoperative injections	4.08 ± 1.74	4.22 ± 1.37	.99
P value	.28	.85	
Median days from last injection to surgery (25th,75th percentile)	15 (3.75, 29)	11 (4, 22)	.65

BCVA = best-corrected visual acuity; CST = central subfoveal thickness.
Asterisk (*) indicates statistical significance.

improvement in visual acuity. The study mentions that the fluid status preoperatively was not assessed, as not all patients had OCTs at study visits and fluorescein angiograms were only performed at routine intervals.[24]

Kessel and associates reported that 89 eyes with neovascular AMD that underwent cataract extraction showed an improvement in visual acuity with no need for increased injection frequency following cataract surgery.[20] The group also identified a different cohort of 19 eyes that had not received an intravitreal injection in over a year prior to cataract surgery. They reported that about half of these eyes (57.9%) required anti-VEGF therapy following surgery at a rate of 0.2 injections per month. They also reported that the eyes actively receiving injections had better outcomes than the inactive patients. There was no mention of the preoperative fluid status of the eyes undergoing cataract surgery.[20] Rappoport and associates published a series of 42 eyes and noted that the eyes injected with anti-VEGF within 1 week of surgery had better visual outcomes immediately after surgery but needed injections sooner after surgery. They also note that eyes with no preoperative fluid had a lower re-injection rate and longer time until the first injection after surgery than the eyes with fluid preoperatively.[25] We report that patients with actively managed wet AMD in a real-life clinical setting improve their BCVA following cataract surgery and this improvement is maintained over 6 months. In our series, for the patients that developed new or worse retinal fluid or hemorrhage, there was no difference in the timing of injections or number of injections preoperatively or postoperatively. This is likely because all of our patients were actively managed with intravitreal injections prior to cataract surgery, which led to a relatively stable postoperative period. The patients without fluid postoperatively also tended to have continued improvement in visual acuity, while those with fluid postoperatively saw an initial improvement in visual acuity that was stable over 6 months.

This study is limited by its retrospective nature and the limited number of patients. At our institution, patients receive imaging at intervals while they are receiving anti-VEGF injections, and this interval was not changed when undergoing cataract surgery. Imaging at 1 month with OCT postoperatively may have shown more patients who had worsening retinal fluid. We did not exclude patients with other underlying ocular conditions such as glaucoma or patients that suffered complications during cataract surgery, which may alternatively affect their visual acuity. This was a study using real-world data, and thus patient compliance to medication regimens and injection intervals fluctuated, which may have biased the results in several manners. At our institution, all patients undergoing cataract surgery are managed with postoperative antibiotics and a prednisolone taper; however, there

are a few cataract surgeons who during this time period did use topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the postoperative course. The use of NSAIDs may have influenced the development of postoperative cystoid macular edema (CME); however, these medications are only used for 4 weeks postoperatively and would not have affected the development of CME later in the postoperative course. Note that in this study, even though, as seen in clinical trials, patients had macular fluid, they were all being actively treated with intravitreal anti-VEGF therapy. Therefore the results may not apply to patients with exudative AMD with macular fluid who are untreated, or who are not being actively injected. It is also worth mentioning that 8 patients had worse visual acuity following surgery and that these patients were more likely to have preoperative macular fluid. Still, 18 out of the 23 patients with fluid preoperatively had improved visual acuity and, taken together, the patients with preoperative macular fluid had a significant improvement in vision at 4-6 weeks postoperatively, which was maintained over 6 months without any difference in the worsening of their underlying AMD.

In conclusion, in a real-world setting, cataract surgery was shown to improve the visual acuity in patients with wet AMD receiving intravitreal anti-VEGF injections. Patients with retinal fluid on OCT preoperatively had a significant improvement in postoperative visual acuity without significant worsening of retinal fluid postoperatively. If a patient has fluid prior to cataract surgery, as long as the patient is actively being injected, there is no difference in outcomes between those patients who had no fluid. Although there is a small risk of developing a subretinal hemorrhage, AMD patients with visually significant cataracts and macular degeneration requiring intravitreal anti-VEGF injections may successfully undergo cataract extraction, even with fluid on the preoperative OCT, without visually significant worsening of their underlying neovascular process.

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