The Effects of Cataract Surgery on Patients With Wet Macular Degeneration

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• PURPOSE: To explore whether cataract surgery contributes to the progression of wet age-related macular degeneration (wet AMD).
• DESIGN: Retrospective cohort study.
• METHODS: Retrospective review was performed of consecutive patients with wet AMD who underwent cataract surgery at the midpoint of a 1-year study window. A control arm included wet AMD eyes treated with anti–vascular endothelial growth factor (VEGF) injections that did not undergo cataract surgery for a 1-year period. Best-corrected visual acuity (BCVA), number of anti-VEGF injections, and optical coherence tomography (OCT) features were compared between the 2 arms.
• RESULTS: Forty eyes in the surgical group and 42 in the nonsurgical group were included. BCVA was equivalent in the first half of the study, and became significantly better in the surgical group vs the nonsurgical group (0.23 ± 0.65 vs 0.11 ± 0.59 logMAR improvement, $P = .049$). There was no change in the number of injections given 6 months before vs after the midpoint in the surgical group ($P = .921$). The mean OCT central retinal thickness became greater in postsurgical eyes compared to nonsurgical eyes (265.4 ± 98.4 μm vs 216.4 ± 58.3 μm, $P = .011$). Surgical eyes were more likely to develop new or worse cystoid changes after the study midpoint (13 surgical eyes [54.2%] vs 9 nonsurgical eyes [28.1%], $P = .048$).
• CONCLUSIONS: Cataract surgery leads to vision improvement and does not appear to contribute to worsening of wet AMD. However, anatomic changes based on OCT analysis suggest a subclinical susceptibility to postoperative cystoid macular edema or exacerbation of choroidal neovascularization. (Am J Ophthalmol 2015;160(3):487–492. © 2015 by Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) AND cataract are common causes of vision loss in our aging population. Recent advances in the treatment of wet AMD have succeeded to either stabilize or improve vision in a large proportion of cases.[1–4] It is therefore not uncommon for wet AMD patients to develop visually significant cataracts. However, there is concern about proceeding with cataract surgery in patients with wet AMD, as there may be a risk of exacerbating choroidal neovascularization (CNV) or progressing geographic atrophy.

There is little evidence in the current literature to aid the decision to proceed with cataract surgery in patients undergoing active treatment for wet AMD. Concern exists that intraocular pressure fluctuations and increased inflammatory mediators associated with uncomplicated cataract surgery may disrupt or further stimulate delicate neovascular vessels. Adverse events related to worsening wet AMD may lead to poorer visual outcome or increased AMD treatment demands, requiring further cost and clinic visits for the patient.

Our study aims to evaluate the visual outcomes and possible complications of cataract surgery in patients with wet AMD. This is the first study to include a control arm and an examination of specific optical coherence tomography (OCT) features.

METHODS

A RETROSPECTIVE COHORT STUDY WAS PERFORMED. A chart review was performed at an urban teaching hospital of all patients from January 2008 through May 2013 with active wet AMD who had undergone cataract surgery. The selected years represent the timeframe in which an electronic medical record was available at the institution. Active wet AMD was defined as eyes that received at least 1 anti–vascular endothelial growth factor (anti-VEGF) injection in the 1-year study window. The eyes that met the criteria formed the surgical cohort. A nonsurgical control group was formed by reviewing the charts of patients in the same health system who were receiving anti-VEGF injections for active wet AMD in the year 2012. Eyes were included if they were phakic and had not undergone cataract surgery in that year. The year 2012 was selected as it represented a time period where the majority of OCT images in the study setting were obtained using a Stratus OCT. Non-Stratus OCTs were not included in quantitative analyses. The "midpoint" of the study was defined as the date of cataract extraction in the surgical group and July 1, 2012 in the nonsurgical group.

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The cases were identified by reviewing the medical records of the practices of 5 retina specialists. The patients were predominately receiving anti-VEGF injections using a treat-and-extend protocol, which has been described in detail elsewhere.[5,6] In brief, eyes were typically treated with an induction phase of 3 consecutive monthly injections and extended based on OCT findings. The study was prospectively approved by the Henry Ford Hospital Institutional Review Board and is in accordance with the principles outlined in the Declaration of Helsinki. Handling of patient data was in compliance with Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Patients with both occult and classic wet AMD were included. Patients were excluded if they had concomitant diagnoses that could contribute to neovascularization, such as proliferative diabetic retinopathy or retinal vascular occlusion. Eyes with significant ocular pathology such as advanced glaucoma or retinal detachment that may limit visual acuity were also excluded. Eyes with complicated cataract extractions were noted and separate analyses were performed both including and excluding these eyes. Data collected from medical records included demographic characteristics and ocular history. The number of anti-VEGF injections, type of anti-VEGF injection administered, and changes in anti-VEGF medication administered were recorded in the 6 months before and after the midpoint. Best-corrected visual acuity (BCVA) was recorded 3 months before and after the midpoint. Central OCT thickness was recorded only in Stratus OCTs in the 3 months before and after the midpoint. Presence of cysts and subretinal fluid on OCT was recorded in the 3 months before the midpoint. Only worsening or new cysts and subretinal fluid were recorded in the 3 months after the midpoint. Qualitative OCT findings were recorded in all OCT types, including Stratus, Cirrus, and Spectralis. The presence of macular hemorrhage on examination or fundus photography in the 3 months before and after the midpoint was noted. The presence of subfoveal atrophy was noted on OCT, examination, or fundus photography 3 months before, 3 months after, and 6 months after the midpoint.

The data were collected and entered into a computerized database (Excel 2013; Microsoft Corporation, Redmond, Washington, USA). All eligible patients in the surgical group were included in the database. Eyes eligible for the control group were far more prevalent, so a representative sample was taken. The list of eligible control eyes was randomized using the "randomize list" function in Excel. Eyes were then included consecutively from the list until a group of comparable size was formed.

For statistical analysis, SAS software version 9.2 (SAS Institute, Cary, North Carolina, USA) was used. Snellen BCVA was converted to equivalent logMAR values. The group comparisons of the numeric data were performed using the Wilcoxon rank sum test if the distributional normality assumption was violated, otherwise using 2-sample t tests. The group comparisons of the categorical data were performed using the Fisher exact test in the presence of sparse data, otherwise using the χ^2 test. A P value less than .05 was considered statistically significant.

TABLE 1. Distribution of Eyes in Surgical Group (40 Eyes With Wet Age-Related Macular Degeneration That had Undergone Cataract Surgery) Based on Visual Acuity 3 Months Before and After Cataract Surgery

BCVA	3 Months Preoperative	3 Months Postoperative
≥20/40	12 (30%)	20 (50%)
20/50–20/100	21 (53%)	17 (43%)
<20/100	7 (17%)	3 (7%)

BCVA = best-corrected visual acuity.

RESULTS

FORTY OF 40 ELIGIBLE EYES WERE INCLUDED TO FORM THE surgical group (39 patients), and 42 of 179 eligible eyes were included by computer-generated randomization to form the nonsurgical group (38 patients). The mean age in the surgical and nonsurgical groups was 80.8 ± 6.5 years and 79.2 ± 9.1 years, respectively. The majority of patients were white, representing 34 patients (85%) in the surgical group and 28 patients (67%) in the nonsurgical group.

The BCVA at 3 months prior to the midpoint was 0.65 ± 0.64 logMAR (20/89 Snellen acuity) in the surgical group and 0.65 ± 0.90 logMAR (20/89 Snellen acuity) in the nonsurgical group ($P = .097$). The mean change in BCVA was statistically significant between the 2 groups 3 months after the midpoint, with surgical eyes improving 0.23 ± 0.65 logMAR (with improvement to 20/53 Snellen acuity) and nonsurgical eyes improving 0.11 ± 0.59 logMAR (with improvement to 20/69 Snellen acuity, $P = .049$). Table 1 shows the distribution of eyes based on visual acuity 3 months before and after cataract surgery. Table 2 shows the distribution of eyes based on visual acuity 3 months before and after the midpoint in the control group.

There was no significant difference in the number of injections pre- and post-surgery in the surgical group, with eyes receiving 2.31 ± 1.40 injections before and 2.30 ± 1.45 injections after the midpoint ($P = .921$). Nonsurgical eyes received 3.00 ± 1.45 injections before and 2.57 ± 1.45 injections after the midpoint, and this decrease approached statistical significance ($P = .057$). There was no statistically significant difference in the change in the number of injections received by the surgical (−0.03 ± 1.60) and nonsurgical (−0.43 ± 1.42) groups before and after the midpoint ($P = .233$).

In the preoperative period of the cataract extraction group, 28 eyes (70%) were receiving predominantly

TABLE 2. Distribution of Eyes in Control Group (42 Phakic Eyes With Active Wet Age-Related Macular Degeneration That had Received Routine Treatment and Not Undergone Cataract Surgery) Based on Visual Acuity 3 Months Before and After the Midpoint of the Study

BCVA	3 Months Before Midpoint	3 Months After Midpoint
≥20/40	20 (48%)	20 (48%)
20/50–20/100	16 (38%)	18 (43%)
<20/100	6 (14%)	4 (9%)

BCVA = best-corrected visual acuity.

bevacizumab and 12 eyes (30%) ranibizumab. Before the midpoint of the nonsurgical group, 33 eyes (79%) were receiving predominantly bevacizumab and 9 eyes (21%) ranibizumab. There was no significant difference in the proportion of eyes that switched the type of anti-VEGF medication after the midpoint of the study (7 eyes [16.7%] in the surgical group vs 7 eyes [17.5%] in the nonsurgical group, $P > .999$).

Analysis of OCT imaging showed no significant difference in starting central thicknesses between the surgical and control groups (228.8 ± 60.9 μm vs 223.1 ± 60.6 μm respectively, $P = .649$). A significant difference was found in the final central thickness, with surgical eyes measuring 265.4 ± 98.4 μm and nonsurgical eyes measuring 216.4 ± 58.3 μm ($P = .011$). Surgical eyes had significantly more new or worse cysts after the midpoint, with worsening noted in 13 surgical eyes (54.2%) vs 9 nonsurgical eyes (28.1%) ($P = .048$). There was no significant difference in subretinal fluid between the 2 groups, with worsening subretinal fluid in 7 surgical eyes (30.4%) and 4 nonsurgical eyes (12.5%) ($P = .171$). There was also no significant difference in the development of subfoveal atrophy at 3 and 6 months ($P = .187$ and $P = .422$, respectively) or incidence of new macular hemorrhage between the 2 groups ($P = .432$).

A subanalysis was performed comparing surgical eyes to control eyes while excluding surgical cases that had complicated cataract extraction. Reasons for exclusion included anterior vitrectomy, posterior capsular tear, retained lens fragments, or intraoperative floppy iris requiring the use of a Malyugin ring (MicroSurgical Technology, Redmond, Washington, USA). In total, 6 eyes were excluded from the subanalysis. The results again showed no significant difference in the change in the number of injections before and after the midpoint (−0.43 ± 1.42 for the nonsurgical group and −0.03 ± 1.63 for the surgical group, $P = .262$). A significant difference was again found in mean OCT thickness in the second half of the study (216.4 ± 58.3 μm in nonsurgical eyes and 263.0 ± 101.0 μm in surgical eyes, $P = .019$) and the presence of worsening cysts (9 nonsurgical eyes [28.1%] vs 12 surgical eyes [60.0%], $P = .023$). There was no significant difference in the development of subfoveal atrophy, worsening subretinal fluid, worse or new hemorrhage, or change in the administered anti-VEGF medication between the surgical and nonsurgical eyes.

An analysis of statistical power was performed using a sample size of 82 (40 surgical eyes, 42 control eyes) along with a 2-sided alpha level of 0.05. A 2-sample *t* test had a power of 0.80 to detect an effect size of about 0.63. This corresponded to the ability to detect an underlying mean group difference of at least 0.39 logMAR for the pre- to postsurgery change in BCVA and at least 0.95 for the pre- to postsurgery change in number of injections. Furthermore, using the sample size along with a 2-sided alpha level of 0.05, the χ^2 test had a power of 0.80 to detect a mean rate difference between the 2 groups of about 8% vs 32% for a characteristic that was present in 20% of the total study sample.

DISCUSSION

THE PREVALENCE OF BOTH CATARACT AND AGE-RELATED macular degeneration is growing in our aging population. Both conditions are thought to have similar risk factors, including age, light exposure, inflammation, prior surgery, or other conditions that contribute to the breakdown of the blood-retinal barrier. It is therefore not surprising that cataract and age-related macular degeneration may co-contribute to visual impairment and lead to questions regarding the best intervention, if any, to maximize visual outcome.

Prior studies have been inconclusive in demonstrating whether cataract surgery worsens dry AMD. Early studies have reported that the rate of progression of dry AMD appears to occur more rapidly in operated eyes compared to the fellow eye.[7,8] Other studies, including the Blue Mountains Eye Study, have shown an increased association of cataract surgery with the incidence of advanced dry AMD.[9,10] The Blue Mountains Eye Study reported an odds ratio of 5.7 for progression to advanced AMD in surgical eyes vs nonsurgical eyes.[9] In contrast, Armbrecht and associates found that cataract surgery led to better visual function and quality-of-life measures for patients with mild to moderate dry AMD (long-term outcomes were not examined).[11,12] The risk of progression found in older studies may be related to older cataract surgery techniques and intraocular lens designs.[13] An analysis of the Age-Related Eye Disease Study eyes that underwent cataract surgery was performed by Chew and associates,[14] who defined worsening of dry AMD as conversion to wet AMD, onset of geographic atrophy, or central-involving geographic atrophy. The results showed no clear effect of cataract surgery contributing to progression.[14]

The risk of progression of dry AMD to wet AMD has been examined by a number of investigators, and an association has not been found in cross-sectional and retrospective case-control studies.[15,16] Dong and associates[17]

prospectively examined a series of 108 patients with dry AMD undergoing cataract surgery and found an incidence rate of wet AMD of 12.7%. However, after excluding the cases classified as wet AMD in the first month, this number dropped to 4.6% at 1 year. The authors concluded that the majority of wet AMD seen after cataract surgery is attributable to lens opacity precluding an accurate diagnosis preoperatively. Another randomized controlled trial did not show that cataract surgery in high-risk dry AMD eyes led to the formation of CNV.[18]

There have been far fewer studies to examine the effect of cataract surgery in patients with wet AMD, especially in the era of anti-VEGF therapy. Rosenfeld and associates performed an analysis of ANCHOR and MARINA study patients that underwent cataract surgery.[19] They showed that ranibizumab-treated eyes saw improvement after cataract surgery by a mean of 10.4 ± 3.4 letters, and the change was not statistically different from the fellow eye, or from non-ranibizumab eyes that had undergone cataract surgery. Treatment requirements between the injected eyes were no different, given the monthly injection protocol. In a retrospective case-series study, Tabandeh and associates[13] found no difference in the anti-VEGF requirements of 30 eyes in the time periods before and after cataract surgery, with statistically significant improvement in visual acuity. Furthermore, there were 2 instances of submacular hemorrhage in the study, 1 at 6 months after cataract surgery and 1 at 11 months. These were thought to not be related to the cataract surgery.[13] In a retrospective noncomparative study that included 16 eyes, Muzyka-Wozniak found a stable improvement in BCVA after cataract surgery, with a median follow-up time of 14 months.[20] Time intervals between anti-VEGF injections were unchanged before and after cataract surgery. In another retrospective noncomparative study that included 30 eyes, Grixti and associates similarly found improved BCVA after cataract surgery in patients with wet AMD, with a transient increase in mean OCT thickness.[21] The increased thickness returned to baseline 3 months postoperatively.

In the current study, the results demonstrate that cataract surgery leads to improved BCVA in patients with active wet AMD, and did not increase anti-VEGF treatment requirements. We observed no significant difference in adverse outcomes such as macular hemorrhage or the development subfoveal atrophy within the study window. Our control group of eyes with wet AMD that did not undergo cataract surgery showed, on average, a decrease in the number of injections administered in the second half of the study compared to the first (2.57 ± 1.4 vs 3.00 ± 1.45, $P = .057$). We believe that this nearly statistically significant reduction represents the tendency of providers to treat and extend eyes that are routinely receiving anti-VEGF injections. On the other hand, we note that the surgical group's average number of injections remained unchanged before and after the midpoint (2.31 ± 1.40 injections vs 2.30 ± 1.45, $P = .921$). We postulate that this difference between the 2 groups could represent either the tendency for eyes receiving anti-VEGF treatment to be more difficult to extend owing to increased postoperative macular edema, or a tendency for providers to avoid attempting to extend anti-VEGF treatment in the perioperative period.

OCT analysis showed that the mean central thickness increased and presence of cysts worsened in the 3 months after cataract surgery. It is therefore possible that OCT features may be precluding providers from extending the interval between injections after surgery. Muzyka-Wozniak similarly noted a transient 3-month increase in mean central thickness in eyes with wet AMD undergoing cataract surgery.[20] Our study did not follow OCT features in surgical eyes beyond the 3-month postoperative period. It is therefore unclear if these anatomic changes represent a transient contribution of pseudophakic cystoid macular edema (CME) or worsening of wet AMD. Anti-VEGF treatments are likely beneficial for either pathology.[22–24]

It is important to corroborate these findings in future studies to see if the observed postoperative OCT changes are transient or represent the onset of persistent macular edema. Routine postcataract surgery fluorescein angiography was not performed to distinguish between postoperative CME and CNV secondary to wet AMD. If the changes represent CME, perhaps more uniform use of combined topical steroids, subconjunctival steroids, and topical nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce or eliminate the OCT findings.[25,26] Persistent macular edema may have more profound implications besides loss of acuity, affecting other features of vision such as contrast sensitivity or color perception. Protecting these features may be of particular importance in advanced wet AMD with limited visual potential. However, despite the OCT features of postoperative intraretinal fluid, eyes that underwent cataract surgery were found to have a sustained improvement in vision with ongoing anti-VEGF therapy.

Although intraoperative intravitreal bevacizumab has been used with good visual and OCT-measured outcomes,[27,28] these studies lacked controls, making it difficult to elucidate the efficacy of 1 intraoperative dose vs the need for more intensive therapy in the perioperative period. Furthermore, a better understanding of the changes observed on OCT may help guide whether intraoperative anti-VEGF therapy is more beneficial than the use of perioperative steroids and topical NSAIDs in wet AMD eyes.

Although this study shows that cataract surgery may be performed safely in the context of wet AMD, our results reflect a cautious practice pattern in which only the most stable eyes are allowed to proceed with cataract extraction. Clinical application of these findings should occur in a similar context, as the effect of cataract surgery in uncontrolled wet AMD eyes was not studied, and such a study would likely be unethical.

Limitations of the study include its retrospective design and nonequivalent study groups. In the first half of the study, the control group averaged more injections than

the surgical group, receiving 3.00 ± 1.45 injections vs 2.31 ± 1.40 injections, respectively. Additionally, there were more white patients in the surgical group compared to the control group. These limitations would best be addressed by a larger future prospective, randomized study.

In summary, this retrospective consecutive series with a nonsurgical control cohort suggests that cataract surgery may be safe and efficacious in eyes undergoing anti-VEGF injections for wet AMD, yielding significant visual acuity improvement. However, careful close monitoring is recommended, given that there was a trend toward increased central macular thickness as well as the presence or worsening of intraretinal cysts in the 3 months following surgery.

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Biosketch

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