Phacoemulsification Does Not Induce Neovascular Age-Related Macular Degeneration

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PURPOSE. To investigate whether cataract surgery by phacoemulsification induces progression of early age-related macular degeneration (AMD) to neovascular AMD.

METHODS. Retrospective case-control study. Included were consecutive patients who had undergone phacoemulsification from January 2000 to February 2006 at the Recklinghausen Eye Centre, who had a preexisting diagnosis of early AMD and who were followed up for at least 1 year after surgery (n = 1152 eyes of 696 patients). The control group comprised phakic patients diagnosed with early AMD from January 2000 to February 2006, who did not undergo eye surgery and were followed up for at least 1 year (n = 334 eyes of 202 patients).

RESULTS. At baseline, control eyes had significantly better visual acuity than those of patients who were going to have cataract surgery (0.30/0.35 ± 0.34 vs. 0.40/0.49 ± 0.34, respectively; median/mean ± SD: P < 0.001, Mann-Whitney rank sum test). After 1 year, visual acuity in the control group was worse than in surgical eyes (0.30/0.39 ± 0.38 vs. 0.20/0.26 ± 0.30, respectively; median/mean ± SD: P < 0.001, Mann-Whitney rank sum test). In the cataract surgery group, neovascular AMD developed in 28 (2.43%) of 1152 eyes in the first postoperative year. In the control group, it developed in 6 (1.74%) of 344 eyes of 202 patients. The incidence of neovascular AMD within 1 year was not significantly different between the two groups (P = 0.57, odds ratio 1.30, 95% CI 0.52–3.24, logistic regression analysis, adjusted for age and baseline visual acuity).

CONCLUSIONS. The results indicate that cataract surgery in eyes with early AMD is not a causative factor in neovascular AMD.


Cataract is the most frequent eye disease of elderly people.1 Surgical removal of the cataractous lens by phacoemulsification and implantation of an intraocular lens is considered a safe and effective procedure, and cataract surgery is the most frequently performed surgical intervention worldwide. Age-related macular degeneration (AMD) is the most frequent cause of legal blindness in Western countries.2,3 Despite recent advances, treatment of AMD is mainly limited to late-stage neovascular disease with unsatisfying results. Comorbidity for both diseases in the elderly population is high.

The occurrence of choroidal (i.e., subretinal) neovascularization is the hallmark of neovascular AMD and an ominous sign of disease progression. It is usually associated with severe loss of visual acuity. Various articles have raised concerns that cataract surgery may constitute a risk factor for the development of neovascular AMD,4–9 particularly in patients with early AMD.6 This possibility raises serious ethical, clinical, economic, and legal issues for the ophthalmologist treating patients with cataract and early AMD. In contrast, several studies have shown a sustained improvement of visual function after cataract surgery in patients with early AMD.10–15 In theory, cataract surgery may have an indirect adverse effect because removal of the crystalline lens may leave the retina more susceptible to damage through light, which it normally absorbs. Although all intraocular lens implants used today have UV-filtering properties, this theoretical concern has recently led to the development of intraocular lens implants that additionally absorb blue light (‘yellow’ lenses).14 However, cataract surgery may itself have a direct effect on progression of early AMD. Hypothetically, several distinct mechanisms are possible (e.g., mechanical, by inducing intraocular pressure changes causing trauma to the retina and/or choroid). An eye with early AMD may be especially vulnerable to trauma because Bruch’s membrane is altered. Acute or chronic postoperative inflammation may act as an additional angiogenic stimulus. Proinflammatory chemokines involved in increasing permeability and edema formation also have angiogenic properties.15 Subclinical cystoid macular edema (CME) is reported to occur in 10% to 20% of cases after uncomplicated cataract surgery,16,17 possibly facilitating choroidal neovascularization. There is some circumstantial support for this hypothesis because vascular endothelial growth factor (VEGF) antagonists, which are used in the treatment of choroidal neovascularization, have also been used successfully for treatment of CME.18

It was our intent in this retrospective study to investigate whether cataract surgery by phacoemulsification induces progression of early AMD to neovascular AMD.

METHODS

The study complied with the tenets of the Declaration of Helsinki. Included were consecutive patients who had undergone phacoemulsification from January 2000 to February 2006, had a preexisting diagnosis of early AMD (defined below), and were followed up for at least 1 year after surgery. All patients underwent phacoemulsification in the Recklinghausen Eye Centre and received a standard intraocular lens (IOL) with ultraviolet protection. Standardized phacoemulsification was performed by three experienced surgeons (HB, GBS, DdO). There is a routine follow-up schedule for all patients who have cataract surgery: postoperative days 1, 7, and 14 and 6 weeks, 6 months, and 1 year. Every patient is advised to have immediate examinations if reduced visual acuity or metamorphopsia occurs.

The control group comprised all phakic patients who had early AMD diagnosed from January 2000 to February 2006, who had not undergone eye surgery within 1 year after the diagnosis of AMD was made, and who were followed up for at least 1 year. In control eyes,
cataract surgery was not performed, either because the patient did not want surgery or the gain in visual acuity, as estimated by the ophthalmologist, was considered low. This limited expectation was the case in eyes with either minor lens opacification or where fundus examination suggested macular degeneration to be the major cause of reduced visual acuity.

**Review of Electronic Medical Records**

Patients included in the study were identified in a database search of the medical record database of the Eye Center (electronic medical office software; ifa Systems, Cologne, Germany).

Identifying patients relevant for this study included a two-step process: First, the database was searched automatically for relevant diagnoses. From January 2000 to February 2006, 9,375 patients (14,318 eyes) underwent cataract surgery. Individual electronic medical records (EMRs) of each patient were then reviewed. This was facilitated by the exclusive use of the EMR for record keeping. Early AMD was defined as the presence of soft drusen, pigmentary abnormalities consistent with AMD, and absence of choroidal neovascularization. When biomicroscopic examination raised the suspicion of subretinal fluid or membranes and unless lens opacification was too dense to allow further fundus examination, fluorescein angiography was performed to rule out leakage from choroidal neovascularization. Fluorescein angiography was performed in cases of doubt. In the entire group of patients with a funduscopic diagnosis of early AMD who had undergone phacoemulsification, 177 eyes had preoperative fluorescein angiography. Eyes with central retinal disease other than AMD (e.g., myopic maculopathy, proliferative diabetic retinopathy, and retinal vein occlusion) were excluded. Only those patients who attended regularly for follow-up for at least 1 year after surgery were included in the study. Some patients had follow-up examinations by their referring ophthalmologists. Again, any funduscopic suspicion of neovascular AMD was considered an indication for fluorescein angiography. Three hundred twenty-four eyes had fluorescein angiography within the first year after surgery. In 28 of these eyes, neovascular AMD was confirmed.

In the control group, 97 of 344 eyes had had fluorescein angiography when early AMD was diagnosed. Of the six eyes in the control group in which neovascular AMD developed within the first year after a diagnosis of early AMD was made, four eyes had had previous fluorescein angiography showing early AMD. In the other two eyes, we had no indication/suspicion of neovascular AMD; therefore, no fluorescein angiography was performed when the diagnosis “early AMD” was made.

**Statistical Analysis**

Statistical analysis was performed with commercial software (SPSS Inc., Chicago, IL). The significance level was defined as $P < 0.05$. The $\chi^2$ test with Yates correction was used for contingency table analysis. Multiple logistic regression was used to estimate the influence of covariables on a dichotomous dependent variable (neovascular AMD diagnosed within 1 year or not).19 Time until diagnosis of neovascular AMD was plotted for patients with cataract surgery and control subjects using the product-limit method of Kaplan and Meier20 and compared using the log rank test.21 The Cox proportional hazards model was used to adjust for the simultaneous effects of age and baseline visual acuity.22

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**Table 1. Age Distribution**

<table>
<thead>
<tr>
<th>n</th>
<th>Mean Age</th>
<th>Median Age</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery 1152</td>
<td>77.9</td>
<td>78.3</td>
<td>55.4–95.2</td>
</tr>
<tr>
<td>Controls 344</td>
<td>74.3</td>
<td>75.1</td>
<td>55.2–92.2</td>
</tr>
</tbody>
</table>

Data are years; $n = \text{number of eyes}$.

**RESULTS**

A total of 1152 eyes with early AMD from 696 patients who underwent phacoemulsification were included in the study; 344 phakic eyes with early AMD from 202 patients served as the control. Table 1 shows the age distribution in both groups. Patients in the surgical group were older than in the control group, and this difference was statistically significant ($P < 0.001$, Mann-Whitney rank sum test).

At baseline, control eyes had a statistically significantly better visual acuity than patients who were going to have cataract surgery ($0.30/0.35 \pm 0.34$ vs. $0.40/0.49 \pm 0.34$, respectively; median/mean $\pm$ SD; $P < 0.001$, Mann-Whitney rank sum test). After 1 year, visual acuity in the control group was worse than in surgical eyes ($0.30/0.39 \pm 0.38$ vs. $0.26/0.26 \pm 0.30$, respectively; median/mean $\pm$ SD; $P < 0.001$, Mann-Whitney rank sum test). In the cataract surgery group, neovascular AMD developed in 28 (2.43%) of 1152 eyes in the first postoperative year. In the control group, it developed in 6 (1.74%) of 344 eyes within 1 year. Figure 1 shows the time points when a new diagnosis of neovascular AMD was made. There was no significant difference between both groups in the incidence of neovascular AMD ($P = 0.57$, odds ratio 1.30, 95% CI 0.52–3.23, logistic regression analysis). The power for the calculated odds ratio of 1.3 was 0.09 ($\chi^2$ test; smallest detectable odds ratio for a power of 0.8 = 2.9).

The Kaplan-Meier curves until diagnosis of neovascular AMD are shown in Figure 2. There was no significant difference in time-to-event between both groups ($P = 0.65$, hazard ratio 1.23, 95% CI 0.50–3.00; Cox regression analysis).

The diagnosis of neovascular AMD after cataract surgery may not be new disease, but may indeed have been facilitated by a better view of the fundus, not representing new onset of neovascular AMD. We therefore tried to determine whether insufficient visualization may actually have played a role, causing preexistent neovascular AMD to be overlooked. Therefore, preoperative medical records and all available fluorescein angiograms of patients with postoperative neovascularization were evaluated for a second time. Reevaluation showed that one eye in which neovascular AMD was diagnosed at day 8
after surgery had an advanced cataract before the operation, which compromised the examination. Three more eyes with diagnosis of neovascular AMD at days 9 and 12 had ambiguous findings in the preoperative angiography. Although these patients could be considered to have had neovascular AMD before cataract surgery, they were retained in the study.

**DISCUSSION**

Phacoemulsification in patients with early AMD did not significantly increase the risk of development of choroidal neovascularization in the first postoperative year. The high number of patients with early AMD who had cataract surgery with regular follow-up examinations in an institution providing surgical and medical retinal care is a major feature of our study. Fluorescein angiography was readily available if fundus biomicroscopy suggested possible neovascular AMD, which explains the relatively high number of angiographic examinations: 324 eyes had fluorescein angiography within the first year of cataract surgery. The high number of angiographic examinations: 324 eyes had fluorescein angiography within the first year of cataract surgery. The high number of angiographic examinations: 324 eyes had fluorescein angiography within the first year of cataract surgery.

As has been stated earlier, the straightforward method of determining whether cataract surgery does indeed trigger development of neovascular AMD would be a prospective randomized trial. However, there are several obstacles: Data from our study suggest the need for a sample size of more than 28,000 patients, to reach a power of 0.8, assuming a similar balance of surgical and control subjects, a similar event rate and follow-up. Also, it would presumably be difficult to deny patients cataract surgery in eyes randomly allocated to the control group. Prospective studies analyzing eyes that underwent cataract surgery and comparing their rate of neovascular AMD with nonsurgical eyes were inconclusive because of the small sample size. Large population-based epidemiologic studies support the hypothesis of an increased risk for neovascular AMD after cataract surgery. However, even large population-based studies have shown only a relatively small number of patients with new neovascular AMD developing within a given window of observation.

Recently, the investigators in two studies have taken another approach: They searched databases for patients with neovascular AMD and analyzed whether and for how long the patients had been pseudophakic. This eliminated the problem of analyzing only small numbers of patients with neovascular AMD. However, if the study sample is drawn only from patients who acquire neovascular AMD, it may be difficult to determine the effect of a risk factor (e.g., cataract surgery). In addition, it would be necessary to determine how many individuals underwent cataract surgery without the development of neovascular AMD. In the two studies, different strategies were chosen to obtain these data: Kaiserman et al. used the diagnosis records of a health maintenance organization (HMO) to find matched control subjects for patients who had had cataract surgery. The patients were matched for age, gender, and chronic diseases (hypertension, hyperlipidemia, diabetes, and ischemic heart disease), but not for the presence or severity of AMD. From this study, it was concluded that patients with cataract surgery had a higher rate of photodynamic therapy (PDT) for neovascular AMD. Several factors limit the value of this study: Data were analyzed per patient, not per eye. Thus, a patient undergoing cataract surgery on his right eye who was later treated for neovascular AMD in his left eye would have been counted as a patient with both conditions in the same eye. The control cases were not matched for retinal disease, especially AMD. This is an important limitation as individual patients may have a different susceptibility for development of AMD. Because the HMO did not cover PDT for other causes of choroidal neovascularization, it was assumed that in all cases, PDT was indicated for subfoveal AMD. This may not have been the case. In another study, cases of subretinal neovascularization of other origin (e.g., angioid streaks, myopia, chorioretinal scars) were found in a search of a database of 3154 angiography reports. Sutter et al. analyzed the difference in lens status (phakic or pseudophakic) in patients with neovascular AMD. No significant difference in lens status was found between eyes with neovascular AMD and fellow eyes with early AMD. Moreover, pseudophakic eyes in which neovascular AMD developed had not been pseudophakic for a significantly longer period. These results are in agreement with our findings. A limitation of our study is that, at baseline, the surgical and nonsurgical patients may have differed in the distribution of clinical subtypes of early AMD. The clinical subtypes of early AMD were not routinely classified and fundus photographs with fluorescein angiography were obtained only when neovascular AMD was suspected during fundus biomicroscopy. Patients in the surgical group were older, and they had worse visual acuity before phacoemulsification. These differences may have introduced a bias, in that patients in the surgical group may have had more advanced stages of early AMD and thus a higher risk of the development of neovascular AMD. Even if this bias existed, it had only a limited effect on our findings, as no significantly increased incidence of neovascular AMD was found in surgical eyes. Correction of this bias may further reduce the effect size. Moreover, the improved visual acuity after surgery suggests little impact of possible prior retinal disease. It has been suggested that obscured vision of the fundus in some patients with cataract causes late-stage AMD to be unrecognized until cataract surgery is performed. This notion is supported by our findings. Four of 28 eyes with postoperative neovascular AMD most probably already had neovascular AMD before surgery. These patients were not excluded from our study because in clinical practice, neovascular AMD was not diagnosed before surgery, and a decision was made to offer cataract surgery. To exclude these patients because in hindsight they had neovascular AMD before surgery would introduce criteria for cataract surgery that cannot be used in the clinical situation, where...
obviously a decision about cataract surgery has to be made when the cataractous lens might interfere with retinal examination. However, it is important to note that this inclusion of these four eyes would result in finding more cases of neovascular AMD in surgical patients. Thus, there may actually have been bias toward a higher incidence of neovascular AMD in patients with cataract when indeed we could not find a significant difference. We selected only patients from our database who had taken follow-up examinations for at least 1 year after surgery. This selection may be a source of bias, if those patients in whom neovascular AMD developed after cataract surgery in our institution chose to seek medical care elsewhere. Although we cannot completely rule out this possibility, it seems unlikely, because the Recklinghausen Eye Centre is the major provider of medical and surgical retina services locally. As it happens, most diagnoses from a search of our database for pseudophakia and AMD were patients who were referred to us with a diagnosis of AMD after having had cataract surgery elsewhere. These patients were not included in the study because there was insufficient information about the severity of AMD before cataract surgery and evolution of their disease.

Our data do not indicate that phacoemulsification constitutes a significant risk of development of choroidal neovascularization (CNV) in patients with early AMD. However, because development of CNV was a rare event even in the large number of patients studied, the power of the study is low, which also shows in the sample size calculation discussed earlier. Calculation of study power and sample size in a retrospective study is only of limited value. However, it may be interesting to analyze the data under the assumption that results of inductive statistics can be ignored and assuming that the difference between groups is indeed real: In analogy to the number needed to treat (NNT), which is widely used in therapeutic trials,28 we can calculate the number needed to harm (NNH) for unwanted side effects. For our data the calculated NNH is 146 patients. In other words: If the differences were real, of 146 patients with early AMD who undergo phacoemulsification, compared with the control group, 1 additional patient would have neovascular AMD develop in the first year after surgery because of the surgery.

In our study, the observation period of 1 year was chosen so that we could detect effects of cataract surgery by phacoemulsification. It was assumed that any direct side effects of the surgical manipulation would appear within 1 year. A longer follow-up might be counterproductive in examining the effect of the surgical procedure, because a contributing effect of pseudophakia (e.g., short wavelength light exposure) would increase with time and may mask the effect of surgery. Therefore, our findings do not allow us to draw any conclusions about possible long-term effects of retinal exposure to increased levels of blue-spectrum light due to pseudophakia. Nor can we draw any conclusions about the course of geographic atrophy after cataract surgery. Because of limits caused by low statistical power, a small effect of cataract surgery may not have been detected by the present study.

In conclusion, our data do not indicate that cataract surgery in eyes with early AMD is a causative factor in neovascular AMD.

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References


