Risk Factors Associated with Persistent Anterior Uveitis after Cataract Surgery

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• PURPOSE: To identify risk factors for the development of persistent anterior uveitis (PAU) following uncomplicated phacoemulsification cataract extraction in patients without histories of uveitis or autoimmune diseases.
• DESIGN: Retrospective cohort study.
• METHODS: Medical records were reviewed of patients who underwent phacoemulsification cataract extraction with intraocular lens implantation between January 1, 2014, and December 31, 2016, at the University of Colorado Hospital. Exclusion criteria included patient history of autoimmune disease and/or uveitis, cataract surgery combined with another intraocular surgery, and complicated cataract surgery. Patients with PAU were identified according to Standardization of Uveitis Nomenclature Working Group criteria. Data including sex, race/ethnicity, surgery length and cumulative dissipated energy (CDE), and postoperative visual acuity (VA) and intraocular pressure (IOP) were obtained. Main outcome measurements were risk factors for the development of PAU.
• RESULTS: The charts of 3,013 eyes from 2,019 patients were reviewed. A total of 61 eyes (2.0%) from 48 patients developed PAU. African Americans were more likely than whites to develop PAU (relative risk = 11.3; $P < 0.0001$). Age, sex, surgery length, and CDE were not risk factors. Patients with PAU did not have worse VA than those without PAU, and African Americans with PAU did not have worse VA or IOP than the other races with PAU. Eighteen of the 61 eyes (29.5%) also developed cystoid macular edema.
• CONCLUSIONS: African Americans have a higher risk of developing PAU after uncomplicated phacoemulsification cataract extraction. The mechanism leading to this is unclear. Although PAU requires prolonged treatment, it does not appear to lead to worse visual outcomes. (Am J Ophthalmol 2019;206:82–86. © 2019 Elsevier Inc. All rights reserved.)

Accepted for publication Feb 9, 2019.
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CATARACT SURGERY IS ONE OF THE MOST COMMON outpatient procedures performed in the United States. There is often mild and self-limiting inflammation after uncomplicated phacoemulsification. Topical steroids or nonsteroidal anti-inflammatory drugs are used to control postoperative inflammation after cataract surgery, as a significant inflammatory response can lead to multiple adverse effects, including cystoid macular edema (CME), changes in intraocular pressure, and formation of anterior or posterior synechiae.[1]

Despite the normally transient nature of postoperative inflammation following cataract surgery, some patients develop a much more chronic or recurrent form of uveitis. Several studies have shown that patients with histories of uveitis are at higher risk for postoperative and recurrent inflammation after cataract surgery.[2–4] Several factors have also been identified that appear to increase the risk of postoperative CME, also known as Irvine-Gass syndrome. These factors include intraoperative iris trauma and severe postoperative inflammation. In contrast, a complete posterior vitreous detachment may be a protective factor.[5] Shorstein and associates[6] found that African-American patients also were at higher risk of Irvine-Gass syndrome. Thus far, no known published studies have investigated the presence of persistent anterior uveitis (PAU) following uncomplicated phacoemulsification cataract extraction in patients without a history of uveitis or autoimmune disease. The purpose of this study was to identify these patients and the pertinent risk factors for PAU.

METHODS

A RETROSPECTIVE COHORT STUDY WAS CONDUCTED BY the use of records from a cataract outcomes registry developed by the Department of Ophthalmology at the University of Colorado School of Medicine. The study prospectively received approval from the Colorado Multiple Institutional Review Board, and all research conformed to the tenets of the Declaration of Helsinki. The registry was used to identify the patients included in this study. Patients who undergo cataract surgery at this academic tertiary care institution have comprehensive reviews of their

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2019.02.016

medical records. Professional research assistants, trained specifically in the abstraction of information related to cataract surgery, reviewed the information from medical charts and entered data into Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, Tennessee) database, a secure, web-based application. The registry includes demographic information, medical history, preoperative medication history, intraoperative and postoperative complications, and preoperative and postoperative eye examinations.

This study included patients who underwent phacoemulsification cataract surgery with intraocular lens implantation between January 1, 2014, and December 31, 2016, at the authors' institution. Exclusion criteria were history of autoimmune disease and/or uveitis, cataract surgery combined with another intraocular surgery (eg, vitrectomy, minimally invasive glaucoma surgery), complicated cataract surgery (defined as posterior capsular tear, vitreous loss, iris trauma, retained lens, zonular dialysis, and/or choroidal hemorrhage), and eyes that did not have at least 3 months of postoperative follow-up. Charts of study subjects were reviewed to determine if they met the definition for a diagnosis of PAU. As designated by the Standardization of Uveitis Nomenclature (SUN) Working Group,[7] PAU was defined as: 1) a grade of at least 0.5+ for anterior chamber cell; 2) continuation of steroid therapy at or beyond the month 3 postoperative appointment; and 3) no other cause found other than postoperative state.

Cataract surgeries were performed using phacoemulsification with clear corneal incisions. Brand moxifloxacin was either injected intracamerally at the end of surgery or placed topically through a soaked collagen shield. Two patients, both white, had iris expansion devices used intraoperatively. Following surgery, patients were typically prescribed a topical postoperative eyedrop regimen consisting of a fluoroquinolone antibiotic, nonsteroidal anti-inflammatory drugs, and steroids. The antibiotic was typically discontinued at the week 1 postoperative appointment. Depending on surgeon preference, the steroid was prescribed as either 1 drop twice daily for 2 weeks (using difluprednate 0.05% [Durezol]) or 4× daily for 1 week, followed by a weekly taper for 3 weeks (using generic prednisolone acetate 1%). However, if there was persistent intraocular inflammation, topical steroids were continued after the month 1 postoperative visit.

The following data were collected: age, race/ethnicity, sex, laterality of surgery, identification as complex surgery, length of surgery, cumulative dissipated energy (CDE) used during phacoemulsification, measurements of visual acuity (VA), intraocular pressure (IOP), grading of anterior chamber cell, presence of CME, and steroid usage at 3, 6, and 12 months postoperatively. Patients were categorized according to self-reported race/ethnicity, which was defined as white, African American, Hispanic, or other. Visual acuity and IOP were determined by a trained, certified ophthalmic technician using Snellen VA at distance viewing and Goldmann applanation tonometry, respectively. The presence and grading of the anterior chamber cell was determined by the physician using the SUN Working Group Grading scheme for Anterior Chamber Cells.[7] Macular optical coherence tomography was ordered at the discretion of the physician.

• **STATISTICAL ANALYSIS:** Incidence of PAU for patients was defined as a diagnosis of either unilateral or bilateral PAU. Relative risk and associated confidence intervals (CI) were calculated for patient-level characteristics. Comparisons of eye characteristics were performed using logistic regressions with general estimating equations (GENMOD; SAS, Inc., Cary, North Carolina) to account for the intrasubject correlation for patients who had both eyes included in the analyses. *P* values less than 0.05 were statistically significant. Statistical analysis was performed using SAS version 9.4 software (Cary, North Carolina).

RESULTS

THERE WERE 5,674 EYES IN THE CATARACT OUTCOME REGISTRY for the specified time period. A total of 2,661 eyes were excluded using the criteria described. A total of 3,013 eyes from 2,019 patients were included in the study. Of these 2,019 patients, 56.6% (1,143) were female, and the average age was 69.5 years old; 73.5% (1,483) were white, 8.5% (172) were African American, and 8.1% (163) were Hispanic (Table 1). A total of 118 eyes were found to meet criteria 1 and 2 (see above) for development of PAU. Of those, 57 eyes were found to have an alternative cause for the persistent inflammation (eg, sarcoidosis, syphilis), or patients were continuing steroid therapy for other reasons (eg, ocular surface disease), or they had additional intraocular surgery in the follow-up period (eg, retinal detachment repair, intraocular lens exchange). Therefore, 61 eyes from 48 patients met full criteria for postoperative PAU: 38 African American, 19 whites, 3 Other, and 1 Hispanic. The overall incidence of postoperative PAU eyes was 2.0% (61) or (48) 2.4% of patients. No patients were noted to have granulomatous inflammation. Eighteen of the 61 eyes (29.5%), including 8 African-American eyes, developed postoperative CME.

Age, sex, CDE, and length of surgery were not significant risk factors for the development of PAU (Tables 1 and 2). Conversely, the presence of PAU was strongly associated with race. Specifically, African Americans were more likely to develop PAU than whites (RR, 11.3; 95% CI, 6.4-20.2; $P < 0.0001$). In addition, all 13 patients with bilateral PAU were African Americans. Comparing eyes that developed PAU, there were no statistically significant differences between African Americans and other races/ethnicities with regard to preoperative use of prostaglandin analogs or brimonidine eyedrops, use of intracameral brand

TABLE 1. Demographic Characteristics of the Study Patients by Uveitis Status

	Total Patients	Unilateral PAU	Bilateral PAU	Incidence PAU[a]	Relative Risk (95% CI)	*P* Value[b]
	2,019	35 (1.7%)	13 (0.6%)	2.4%	-	-
Sex						
Males	876 (43.4%)	15 (1.7%)	7 (0.8%)	2.5%	1.1 (0.6-1.9)	
Females	1,143 (56.6%)	20 (1.8%)	6 (0.5%)	2.3%	Reference	0.7293
Race/ethnicity						
Whites	1,483 (73.5%)	19 (1.3%)	0 (0%)	1.3%	Reference	
African Americans	172 (8.5%)	12 (7.0%)	13 (7.6%)	14.5%	11.3 (6.4-20.2)	<0.0001
Hispanics	163 (8.1%)	1 (0.6%)	0 (0%)	0.6%	0.5 (0.1-3.6)	
Other	201 (10.0%)	3 (1.5%)	0 (0%)	1.5%	1.2 (0.4-3.9)	
Mean ± SD age	69.5 ± 10.6	69.1 ± 7.6	73.2 ± 8.6	70.2 ± 8.0	-	0.5089

CI = confidence interval; PAU = persistent anterior uveitis; SD = standard deviation.

[a]Unilateral and bilateral PAU were combined to get incidence rates for PAU.

[b]Obtained from patient-level chi-square test results for categorical variables and *t*-test results for patient age, comparing patients with unilateral or bilateral PAU to patients without PAU.

TABLE 2. Characteristics of Surgery and Postoperative Outcomes for Eyes by Uveitis Status

	No PAU	PAU	Odds Ratio (95%CI)	*P* Value
Number of eyes	2,952	61		-
CDE				
n	2,651	55		
Mean ± SD	8.8 ± 9.0	6.8 ± 4.1	0.96 ± 0.91-1.00	0.0648
Median	6.3	5.8		
Surgery length (min)				
n	2,569	60		
Mean ± SD	20.2 ± 11.2	21.6 ± 11.4	1.01 ± 0.99-1.03	0.3409
Median	17.0	18.5		
logMAR at mo 3				
n	2,779	61		
Mean ± SD	0.108 ± 0.28	0.117 ± 0.18	1.11 ± 0.64-1.91	0.7150
Median	0.000	0.000		
IOP (mm Hg) at mo 3				
n	2477	56		
Mean ± SD	13.2 ± 2.7	14.3 ± 3.2	1.13 ± 1.03-1.24	0.0070
Median	13.0	14.0		

CDE = cumulative dissipated energy; IOP = intraocular pressure; PAU = persistent anterior uveitis; SD = standard deviation.

moxifloxacin at end of surgery, immediate postoperative steroid regimen, surgery length, or CDE (Table 3).

Patients with PAU did not show statistically significant differences in VA at 3 months compared to those without PAU. There was a small statistically significant difference in IOP; that is, those with PAU had a mean IOP 1.1 mm Hg higher (95% CI: 1.03-1.24; $P = 0.0070$). There were no statistically significant differences in VA or IOP at final follow-up between African Americans and other races with PAU. African Americans were more than twice as likely to have continued inflammation at 1 year postoperatively, although this difference in PAU duration was not statistically significant. Additionally, no statistically significant differences were found regarding the severity of anterior chamber inflammation at the 3-month follow-up between African Americans and other races. A total of 52 of the 61 eyes had 12 months of follow-up. Only 9 of these 52 eyes were still receiving steroid therapy at that time (8 African American eyes and 1 white eye). Of those 9, 3 eyes had epiretinal membranes, and 5 had posterior capsular opacification. No eyes had IOP changes or formation of synechiae.

TABLE 3. Characteristics of Surgery; Postoperative Outcomes, and Steroid Use by Race/Ethnicity for Patient Eyes with Uveitis

	African Americans	Other Races/ Ethnicities	*P* Value
Number of eyes	38	23	-
CDE			
Mean ± SD	7.2 ± 4.6	5.6 ± 2.5	0.1752
Median	6.8	5.0	
Surgical length (min)			
Mean ± SD	20.6 ± 9.7	22.9 ± 13.8	0.4892
Median	19.0	17.5	
logMAR at final follow-up			
Mean ± SD	0.1456 ± 0.18	0.0793 ± 0.13	0.1249
Median	0.0970	0.0000	
IOP (mm Hg) at final follow-up			
Mean ± SD	14.6 ± 2.9	13.7 ± 3.0	0.2482
Median	15.0	14.0	
Postoperative steroid			
Prednisolone acetate 1%	30 (79.0%)	20 (87.0%)	0.4780
Difluprednate 0.05%	8 (21.0%)	3 (13.0%)	
Time to resolution			
Resolved within 1 y	23 (63.9%)	16 (84.2%)	
Not resolved within 1 y	13 (36.1%)	3 (15.8%)	0.1549
Lost to follow-up[a]	2	4	

CDE = cumulative dissipated energy; IOP = intraocular pressure; SD = standard deviation.

[a]Eyes lost to follow-up were excluded from the statistical analysis to obtain a *P* value.

Most PAU patients were treated with additional topical steroids, although 6 eyes (5 African Americans) were also treated with sub-Tenon triamcinolone acetonide injections, and 1 African-American patient's eye was treated with an intravitreal dexamethasone implant.

DISCUSSION

SOME LEVEL OF INFLAMMATION IS EXPECTED TO OCCUR AFter routine phacoemulsification cataract surgery. However, a small number of patients experience a more severe or prolonged course that requires long-term treatment. This study suggests that the risk of developing PAU is associated with race, specifically African-American race. Although no published studies to date have shown a racial predilection for PAU following routine uncomplicated phacoemulsification cataract surgery in patients without a history of autoimmune disease or uveitis, there have been reports with similar associations. For example, Shorstein and associates[6] found that African Americans were at higher risk for post-cataract extraction CME. A recent paper from the authors' institution found that African Americans were at higher risk for PAU following uncomplicated phacoemulsification cataract surgery combined with endoscopic cyclophotocoagulation (RR, 3.08; $P < 0.0001$).[8]

What caused this higher incidence of PAU in African Americans is unclear. The present study did not find an association with PAU and CDE or length of surgery, and African Americans with PAU were not more likely to have required higher CDE or longer surgeries than whites with PAU. One explanation that could explain the higher PAU incidence among African Americans is the increased amount of melanin in African-American eyes. Melanin has been previously shown to augment intraocular inflammation.[9] In addition, an experimental uveitis that resembles human acute anterior uveitis can be induced in certain rat strains by injecting bovine ocular melanin.[10]

An argument could also be made that PAU is due to a recurrent infection with herpes simplex virus (HSV), brought about by the trauma of surgery rather than a truly "idiopathic" condition. However, no published reports were found implicating race as a risk factor for recurrent HSV iritis, and a study by the Herpetic Eye Disease Study Group[11] found that race was not associated with an increased risk of HSV keratitis recurrence.

It has also been postulated that PAU could be due to retained lens fragments following phacoemulsification. There is no evidence, however, that suggests African Americans are more likely to have retained lens fragments. Additionally, using an endoscopic cyclophotocoagulation endoscope, Edmiston and associates[8] did not appreciate retained macroscopic lens particles in any of their patients following lens removal. Another possibility is that intraoperative iris manipulation contributes to PAU. As mentioned above, there is no evidence that suggests iris manipulation is more common in patients of certain races, and there were no statistically significant differences between races in regard to use of intraoperative pupil expansion devices in this study. It is possible, however, that African Americans mount a more robust inflammatory response to retained microscopic lens fragments or iris manipulation, which is perhaps again related to melanin as described previously. Further studies will be needed to better elucidate this phenomenon.

The main limitation of this study is its retrospective nature. However, this retrospective study design did allow for a large sample size and ability to obtain sufficient data for African Americans, who compose only a small portion of our patients. In addition, the large relative risk demonstrated in the present study indicates a very strong association between race and development of PAU following phacoemulsification. Another limitation is the lack of a uniform corticosteroid eyedrop regimen in the immediate

postoperative period. Also, generic corticosteroid eyedrops are known to vary in efficacy. However, there were no differences between African Americans and whites with PAU in regard to postoperative steroid regimen. Additionally, the incidence of postoperative CME in these patients may be understated in this study, as not all patients underwent optical coherence tomography testing. Although African Americans were at higher risk for developing PAU, the present study did not see an association with worse VA or IOP than other races who also developed PAU, although the power was limited to identify these differences. Additionally, patients with PAU did not have worse VA than those who did not develop PAU, suggesting that prolonged postoperative inflammation may not be detrimental to long-term visual outcomes.

In summary, there is a clear association between persistent intraocular inflammation after cataract surgery and African American race. Our study identified no other risk factors for this increased incidence. Awareness of this risk may lead to modification of postoperative corticosteroid regimens in African American patients, although there are currently no data for the effect of altering postoperative management. The mechanism leading to this elevated risk for inflammation is unclear, and further investigation may lead to improved preventative measures.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

Funding/Support: Supported by a challenge grant to the Department of Ophthalmology from Research to Prevent Blindness; the Frederic C. Hamilton Macular Degeneration Center; and the Colorado Clinical and Translational Sciences Institute with the Development and Informatics Service Center from US National Institutes of Health/National Center for Research Resources. The sponsors and funding organizations had no role in the design or conduct of this research.

Financial Disclosures: The authors indicate no financial support or financial conflict of interest.

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