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Effect of Prior Anti–VEGF Injections on the Risk of Retained Lens Fragments and Endophthalmitis after Cataract Surgery in the Elderly

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Purpose: To investigate the effect of prior intravitreal anti–vascular endothelial growth factor (VEGF) injections on surgical and postoperative complication rates associated with cataract surgery in a nationally representative longitudinal sample of elderly persons.

Design: Retrospective, longitudinal cohort analysis.

Participants: A total of 203 643 Medicare beneficiaries who underwent cataract surgery from January 1, 2009, to December 31, 2013.

Methods: By using the 5% sample of Medicare claims data, the study assessed risks of 3 adverse outcomes after receipt of cataract surgery for beneficiaries with a history of intravitreal injections. Risks of these outcomes in beneficiaries with a history of intravitreal injections relative to those without were calculated using the Cox proportional hazard model.

Main Outcome Measures: The primary outcome was the risk of subsequent removal of retained lens fragments (RLFs) within 28 days after cataract surgery. Secondary outcomes were a new diagnosis of acute (<40 days) or delayed-onset (40+ days) endophthalmitis and risk of a new primary open-angle glaucoma (POAG) diagnosis within 365 days after cataract surgery.

Results: Prior intravitreal anti-VEGF injections were associated with a significantly increased risk of subsequent RLF removal within 28 days after cataract surgery (hazard ratio [HR], 2.26; 95% confidence interval [CI], 1.19–4.30). Prior injections were also associated with increased risk of both acute (HR, 2.29; 95% CI, 1.001–5.22) and delayed-onset endophthalmitis (HR, 3.65; 95% CI, 1.65–8.05). Prior injections were not a significant indicator of increased risk of a new POAG diagnosis.

Conclusions: A history of intravitreal injections may be a risk factor for cataract surgery–related intraoperative complications and endophthalmitis. Given the frequency of intravitreal injections and cataract surgery, increased preoperative assessment, additional intraoperative caution, and postoperative vigilance are recommended in patients with a history of intravitreal injections undergoing cataract extraction. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

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Intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents have revolutionized the treatment of retinal diseases and, along with cataract surgery, are the most common ophthalmologic procedures performed in the United States.[1] Analyses of anti-VEGF injection-associated adverse events have generally focused on systemic complications, particularly thromboembolic events, and intraocular complications, including endophthalmitis, inflammation, retinal detachment, and elevated intraocular pressure (IOP).[2,3]

There are a few published individual reports of needle penetration into the lens resulting in subclinical and rapid cataract-inducing lenticular trauma after intravitreal injection.[4–7] A single case of "lens trauma" was reported in the combined Phase 3 data of the pivotal Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD trials after a total of 754 ranibizumab (Lucentis; Genentech, Inc, San Francisco, CA) injections for treatment of neovascular AMD.[8,9] However, the impact of intravitreal injections on surgical complications associated with cataract surgery has not been rigorously investigated in large studies.

In addition to lenticular trauma, there is evidence that repeated intravitreal injections may be associated with sustained elevation of the IOP, which may secondarily increase rates of open-angle glaucoma.[10–12] Cataract extraction can result in a decrease in IOP[13] and offset this elevation. In addition, post-injection antibiotics, which were routinely administered until a recent paradigm shift away from their use after demonstration of a secondary

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Table 1. List of Study Codes

Condition		Administrative Code*
Cataract surgery	CPT-4:	66984, 66982
Intravitreal injection of anti-VEGF agent	CPT-4:	67028 with C9399, J3490, J3590, J2503, J9035, Q2024, C9257, C9233, J2778, Q2046, C9291 on the same claim
Outcomes		
Removal of RLF	CPT-4:	66850
POAG	ICD-9-CM:	365.1x
Endophthalmitis	ICD-9-CM:	360.0x
Exclusion restrictions		
Intravitreal injection of corticosteroid	CPT-4:	67028 with J3300, J3301, J3302, J7312, J1100, C9256, J1094 on the same claim
Pars plana vitrectomy	CPT-4:	67036, 67038, 67039, 67040, 67041, 67042, 67043, 67108, 67112, 67113
Gas pneumatic retinopexy	CPT-4:	67110
Traumatic cataract	ICD-9-CM:	366.2x
Cataract 2/2 ocular disorders	ICD-9-CM:	366.3x
Cataract associated with other disorders	ICD-9-CM:	366.4x
Infantile/congenital cataract	ICD-9-CM:	366.0x
Coexisting conditions		
Pseudoexfoliation	ICD-9-CM:	366.11
Diabetes mellitus	ICD-9-CM:	250.xx
Diabetic retinopathy	ICD-9-CM:	362.0x
Other glaucoma†	ICD-9-CM:	365, 365.0x, 365.2x, 365.3x, 365.4x, 365.5x, 365.6x, 365.7x, 365.8x, 365.9x

CPT-4 = Current Procedure Terminology 4; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; POAG = primary open-angle glaucoma; RLF = retained lens fragment; VEGF = vascular endothelial growth factor.
*Codes are drawn from ICD-9-CM and CPT-4.
†Excludes POAG (ICD-9-CM: 365.1x).

increase in antibiotic-resistant ocular flora,[14,15] may result in an increase in the rate of post-cataract endophthalmitis in eyes with a history of intravitreal injections. These relationships between intravitreal injections and surgical complications, post-cataract surgery endophthalmitis, and post-cataract surgery incidence of primary open-angle glaucoma (POAG) have not been examined in large numbers, which are needed to elicit statistical significance in these rare events.

We used the 5% sample of Medicare claims data to determine the incidence of retained lens fragments (RLFs) requiring subsequent removal (as a surrogate for intraoperative complications), POAG, and both acute (<40 days) and delayed-onset (40+ days)[16] endophthalmitis associated with cataract surgery in patients with and without a history of intravitreal anti-VEGF injections. We provide evidence suggesting that intravitreal injections may be associated with an increased risk of intraoperative complications and endophthalmitis.

Methods

Under a Duke University Institutional Review Board–approved protocol that adhered to the tenets of the Declaration of Helsinki, this study used data from the 2006–2013 Medicare 5% claims and enrollment files provided by the US Centers for Medicare and Medicaid Services on a restricted-access public use basis. This database contains longitudinal information on beneficiary demographic characteristics, diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]), and procedures (Current Procedure Terminology 4 [CPT-4]) from a nationally representative sample of 5% of the total population of Medicare beneficiaries.

The claims files were used to identify Medicare beneficiaries with cataract surgery performed between January 1, 2009, and December 31, 2013 (Table 1). January 1, 2009, was chosen as the earliest date for inclusion in this study to allow a 3-year look-back period, that is, to 2006, the year when the use of anti-VEGF agents had reached widespread use.[17] For this same reason, beneficiaries had to be at least 68 years of age at baseline. Beneficiaries who enrolled in Medicare Advantage, a private alternative to traditional Medicare, were excluded from the analysis sample because claims data are not available for such Medicare beneficiaries. We also excluded beneficiaries who moved outside the United States at any time during the study period. Finally, beneficiaries with diagnoses of traumatic cataract, cataract secondary to ocular disorders, cataract associated with other disorders, infantile/congenital cataract, endophthalmitis, or those with an intravitreal injection of corticosteroids, pars plana vitrectomy, or gas pneumatic retinopexy performed during the look-back period were excluded from the sample. When more than 1 cataract surgery procedure was performed during the study period, the date of the earliest procedure was chosen as the baseline date and the date of the second procedure was treated as a censoring event because it would not be possible to determine which operation or which eye was associated with an observed outcome. To be included in the POAG subsample, an additional restriction of not having a prior diagnosis of glaucoma was imposed. After imposing these restrictions, the final sample sizes were 203 646 for RLF removal/endophthalmitis and 139 656 for POAG (Table 2).