A New Complication Associated with the Use of Prophylactic Intracameral Antibiotics: Hemorrhagic Occlusive Retinal Vasculitis

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Given the substantial increase in antimicrobial resistance among ocular pathogens worldwide, evidence-based strategies are needed to carefully analyze the risks and benefits of routine prophylactic intracameral antibiotics for prevention of infection in cataract surgery. In ophthalmology, 2 basic issues are debated frequently: (1) the effectiveness of intracameral antibiotics in lowering rates of endophthalmitis in association with cataract surgery and (2) the use of vancomycin as a prophylactic antibiotic.

Intracameral antibiotics during cataract surgery, although used in some parts of the world, remain controversial. Prophylactic antibiotics are associated with increased costs, risks to the individual patient, and risks to the population at large, by contributing to the emergence of drug-resistant organisms. In the current issue of Ophthalmology, Witkin et al1 (see http://www.aaojournal.org/article/S0161-6420(16)31231-3/fulltext) illustrate a striking example of risk to the individual patient: they report 36 eyes of 23 patients that demonstrated hemorrhagic occlusive retinal vasculitis associated with intracameral or intravitreal vancomycin used during or shortly after cataract surgery.

In this series, visual outcomes generally were poor despite treatment, with 61% of eyes (22/36) attaining final visual acuity of 20/200 or worse, including 22% (8/36) attaining no light perception. Of note, 7 eyes initially were diagnosed with endophthalmitis and were treated with additional intravitreal vancomycin; of these eyes, 71% (5/7) showed a final visual acuity of no light perception. The subgroup of eyes treated with additional intravitreal vancomycin therefore comprises most (63% [5/8]) of the eyes with no light perception outcomes.

Alternatively, 3 eyes were treated with intravitreal corticosteroids and 2 of these 3 achieved final visual acuities of 20/40 and 20/70. Although the sample size is small, the findings that additional vancomycin is associated with poorer outcomes and that intravitreal corticosteroids are associated with better outcomes collectively support the hypothesis that hemorrhagic occlusive retinal vasculitis represents a delayed-onset hypersensitivity to vancomycin.

Of note, the Centers for Disease Control and Prevention published guidelines that explicitly discouraged the use of vancomycin for surgical prophylaxis in 1995. In 2013, the Centers for Disease Control and Prevention reported that more than half of antibiotics used are either unnecessary or inappropriate and reiterated the recommendation that vancomycin should be reserved for treatment of life- or organ-threatening infections. These concerns illustrate the need for antibiotic stewardship programs.

The rate of acute-onset postoperative endophthalmitis after cataract surgery generally is reported between approximately 0.03% and 0.2%. Some big data retrospective series have reported lower rates associated with the use of intracameral antibiotics, but these studies are limited and likely flawed relating to their study designs in which, generally, an earlier cohort of patients who underwent surgery without intracameral antibiotics is compared with a later cohort of patients who underwent surgery with intracameral antibiotics. Endophthalmitis rates may decline over time for many reasons other than the use of intracameral antibiotics, including improvements in surgical technique, equipment and other factors.

A single randomized clinical trial (RCT) conducted by the European Society of Cataract & Refractive Surgeons in 2007 reported that intracameral cefuroxime was associated with an approximate 5-fold reduction in endophthalmitis rates. This study has been criticized on multiple grounds, including the limited spectrum of activity of cefuroxime, the high rate of endophthalmitis in eyes not randomized to receive intracameral cefuroxime (approximately 0.2%), the use of topical levofloxacin 0.5% beginning 24 hours after surgery (as opposed to the same day), and the use of multiple surgical techniques. Yet, it remains the only published RCT to date on intracameral antibiotics in cataract surgery. We suspect that based on this RCT, the use of intracameral antibiotics has become more common, especially in those nations in which a packaged, approved intracameral cefuroxime preparation (Aprokam; Thea Pharmaceuticals, Clermont-Ferrand, France) is available.

Intracameral cefuroxime currently is not approved in the United States and is unlikely to become approved without a second RCT to support the European Society of Cataract & Refractive Surgeons trial, which is now a decade old. There seems to be a preference among United States cataract
surgeons for this agent: a member survey conducted by the American Society of Cataract and Refractive Surgery in 2014 reported that 69% of members based in nations without access to intracameral cefuroxime would use it if it were available and reasonably priced. Thus, cataract surgeons wishing to use intracameral antibiotics in these nations, including the United States, must use off-label compounded medications. Compounded antibiotics are associated with dilution errors, contaminants, and other risks, as well as regulatory barriers. For example, one series reported *Fusarium* endophthalmitis in 8 consecutive patients operated with extemporaneously compounded cefuroxime formulated for intracameral use from a single bottle of balanced salt solution.

If United States surgeons wish to use intracameral antibiotics, then vancomycin has some advantages, including a broad spectrum of activity against organisms likely to cause acute-onset postoperative endophthalmitis. However, vancomycin has many disadvantages for prophylaxis, including its effects on antibiotic stewardship. Vancomycin, a first-line intravitreal therapy for coverage of gram-positive organisms, is a mainstay in the treatment of endophthalmitis. The Endophthalmitis Vitrectomy Study in 1996 reported that 100% of gram-positive isolates were sensitive to vancomycin. Similarly, the Antibiotic Resistance Monitoring in Ocular Microorganisms study in 2011 reported that 100% of *Staphylococcus aureus* and coagulase-negative staphylococcal isolates were sensitive to vancomycin. Unfortunately, the incidence of endophthalmitis resulting from gram-positive organisms with reduced vancomycin susceptibility or vancomycin resistance seems to be increasing. A recent report reviewed 27 cases of endophthalmitis resulting from organisms with reduced vancomycin susceptibility or vancomycin resistance, including 11 after cataract surgery, and the visual outcomes typically were poor. Hemorrhagic occlusive retinal vasculitis represents a major disadvantage for vancomycin specifically.

In summary, the routine use of prophylactic intracameral antibiotics during cataract surgery, although enticing as a strategy to reduce infection rates, has incompletely proven efficacy, increased costs, possible serious risks to the individual patient, and larger risks to the population as a whole by potentially contributing to antibiotic resistance. Additionally, the recent report herein should alert cataract surgeons to the possibility of introducing a devastating, bilateral, sight-threatening consequence with routine intracameral antibiotics. This well-documented case series also has increased our fundamental understanding of hemorrhagic occlusive retinal vasculitis. Based on currently available safety and efficacy data, as well as cost-effectiveness data, we believe that vancomycin should not be used as a routine via intracameral administration with cataract surgery.

Intraocular vancomycin should be reserved for the treatment of patients with clinically suspected endophthalmitis.

**References**


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**Footnotes and Financial Disclosures**

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