EDITORIAL

Dropless Cataract Surgery: What Are the Potential Downsides?

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CATARACT SURGERY CONTINUES TO EVOLVE, WITH new surgical techniques including clear corneal incision, small-incision surgery, and femtosecond lasers, making it difficult for the published literature to remain relevant to current clinical practices. Despite this ongoing change, one concern has remained constant: endophthalmitis prophylaxis. The use of perioperative povidone-iodine, a lid speculum, and drape with isolation of lids and lashes, as well as a thorough sterile preparation for procedures, is effective in limiting the incidence of endophthalmitis after cataract surgery.[1] The recent advent of "dropless" cataract surgery via the transzonular delivery of TriMoxi or TriMoxiVanc, by Imprimis Pharmaceuticals (San Diego, California, USA), offers a new option for endophthalmitis prophylaxis. As many cataract surgeons consider adopting dropless cataract surgery, it is important to balance the potential adverse issues involved in this technique.

As stated in the product label, TriMoxi is triamcinolone 3.0 mg and moxifloxacin 0.2 mg, and the addition of vancomycin creates TriMoxiVanc. The combination of antibiotic and steroid delivered to the anterior vitreous by transzonular administration during cataract surgery is intended to mitigate the need for postoperative topical medication. The concept of dropless cataract surgery is theoretically attractive for both the prescriber and the patient. Postoperative drops can be corneal toxic, causing ocular surface irritation, and are often expensive. Teaching drop application techniques, as well as dealing with refills and patient noncompliance, can be burdensome on prescribers. Though postoperative drops are less than ideal, this new mode of dropless endophthalmitis prophylaxis contains some inherent downsides.

A clear concern in an era of increased awareness of compounding errors is the need for TriMoxi and TriMoxiVanc to be compounded. Moxifloxacin and vancomycin are not available in a prepackaged form for intracameral use. Recent cases of dilutional errors with intracameral antibiotics have resulted in complications including chronic cystoid macular edema, serous retinal detachment, macular infarction, toxic anterior segment syndrome, and a large outbreak of *Fusarium* endophthalmitis.[2]

The pharmacokinetics of TriMoxi(+/−)Vanc are unclear when placed in the anterior vitreous. Moxifloxacin and other fluoroquinolones have the shortest half-lives of current intravitreal antibiotics being used (1.7 hours), as they are cleared via passive diffusion anteriorly and active transport through the retinal pigment epithelium.[3] Conversely, vancomycin is cleared passively into the anterior chamber when injected intravitreally and has a half-life that has been reported to be 25.1 hours.[4] Routine topical moxifloxacin regimens are able to produce concentrations in the aqueous and anterior vitreous that exceed the minimum inhibitory concentration (MIC) for a week postoperatively.[5] Though the use of intracameral cefuroxime in the European Society of Cataract and Refractive Surgeons (ESCRS) study showed decreased rates of endophthalmitis, all arms of the study used 6 days of postoperative levofloxacin.[6] The proposed removal of the extended coverage provided by a postoperative topical antibiotic to go dropless with TriMoxi(+/−)Vanc, whose pharmacokinetics have yet to be studied, raises the question as to whether the duration of coverage is adequate.

Antibiotic resistance is another consideration when using TriMoxi. Moxifloxacin, a fourth-generation fluoroquinolone, has historically provided a wide spectrum of both gram-positive and gram-negative coverage. Emerging resistance to moxifloxacin has been identified in coagulase-negative *Staphylococcus*, which accounts for approximately 70% of endophthalmitis cases post cataract surgery.[7] A recent review of coagulase-negative *Staphylococcus* causing endophthalmitis at a single university over 20 years revealed that the 5-year mean resistance rate to moxifloxacin has increased from 21% (1995–1999) to 62% (2010–2014).[8]

The use of prophylactic vancomycin in TriMoxiVanc during routine cataract surgery is controversial. The Centers for Disease Control issued guidelines in 1995 specifically discouraging the use of vancomycin in routine

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surgical prophylaxis because of increasing antimicrobial resistance.[9] Vancomycin-resistant enterococci (VRE) is a well-known example. In addition to VRE, there is a documented rise in the MIC of vancomycin in order to treat coagulase-negative *Staphylococcus* causing endophthalmitis, and reports of vancomycin-resistant gram-positive bacterial endophthalmitis have poor visual outcomes.[10] The risk of fueling the emerging resistance to vancomycin for an unproven practice is concerning. Vancomycin remains the most consistent antibiotic in successfully treating gram-positive endophthalmitis cases. Critics of this idea need only to evaluate the published findings of emerging multidrug-resistant bacteria with antibiotic eye drop use after intravitreal injections.[11] Given that there are more than 3 million cataract surgeries performed in the United States each year, exposure of the ocular surface flora to low doses of vancomycin could inadvertently result in an increase in vancomycin-resistant bacteria. Furthermore, recent case reports suggest an association between the use of intracameral vancomycin and the development of postoperative hemorrhagic occlusive retinal vasculitis after uncomplicated cataract surgery.[12]

Another unknown is the risk of steroid-induced ocular hypertension associated with TriMoxi (+/−)Vanc. Steroids are thought to cause alterations in the trabecular meshwork that ultimately lead to decreased aqueous outflow. It is well known that topical steroids can induce ocular hypertension, but drops are easily discontinued, whereas intravitreal steroid depots uncommonly require vitrectomy to remove the offending agent. A recent meta-analysis found that 32% of patients develop ocular hypertension following 4.0 mg of triamcinolone.[13] The dose used in TriMoxi(+/−)Vanc is slightly lower at 3.0 mg. Previous studies at variable dosing of triamcinolone indicate that the ocular hypertension risk is dose dependent.[13,14] Currently there is a paucity of literature addressing transzonular triamcinolone and its associated ocular hypertension risk. Furthermore, the use of triamcinolone diminishes the "wow" effect of cataract surgery, as it leaves patients with obscured vision and floaters for the first week or more. Patient complaints of foggy vision postoperatively have led some cataract surgeons to discontinue the product. Additionally, randomized trials show that topical nonsteroidal anti-inflammatory drugs (NSAIDs) are superior to topical steroids in reducing postoperative pseudophakic cystoid macular edema.[15] Thus, irrespective of the intravitreal steroid and antibiotic used, it is likely that a topical NSAID will need to be prescribed.

Technical and mechanical issues must be considered in addition to the issues of antimicrobial resistance, compounding risks, unclear risk of steroid-induced ocular hypertension, and postoperative foggy vision. In patients with zonular laxity or milder forms of pseudoexfoliation, intraocular lens (IOL) decentration or dislocation may occur. The impact of this technique for premium IOL decentration could create significant visual disturbance. Since most patients using antithrombotics do not discontinue this medication, there could be intraocular hemorrhage from cannula contact with the iris or ciliary body.

Modern cataract surgery is safer for the patient and shorter in duration than in decades past. Improvements in technology, techniques, and training have led to improved outcomes for our patients. Although the concept of dropless cataract surgery is clearly attractive, cataract surgeons should consider the serious issue of declining susceptibilities of microbes to currently available antibiotics and the unnecessary risk of the transzonular delivery of TriMoxi(+/−)Vanc. In an era of increasing cost-benefit analysis where physicians will be judged on outcomes and the allocation of limited healthcare resources, the value of using dropless cataract surgery remains uncertain.

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REFERENCES

1. Packer M, Chang DF, Dewey SH, et al. Prevention, diagnosis, and management of acute postoperative bacterial endophthalmitis. *J Cataract Refract Surg* 2011;37(9):1699–1714.
2. Cakir M, Imamoglu S, Cekic O, et al. An outbreak of early-onset endophthalmitis caused by Fusarium species following cataract surgery. *Curr Eye Res* 2009;34(11):988–995.
3. Iyer MN, He F, Wensel TG, Mieler WF, Benz MS, Holz ER. Clearance of intravitreal moxifloxacin. *Invest Ophthalmol Vis Sci* 2006;47(1):317–319.
4. Aguilar HE, Meredith TA, el-Massry A, et al. Vancomycin levels after intravitreal injection. Effects of inflammation and surgery. *Retina* 1995;15(5):428–432.
5. Chung JL, Lim EH, Song SW, et al. Comparative intraocular penetration of 4 fluoroquinolones after topical instillation. *Cornea* 2013;32(7):1046–1051.
6. Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg* 2007;33(6):978–988.

7. Lalwani GA, Flynn HW Jr, Scott IU, et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. *Ophthalmology* 2008;115(3):473–476.
8. Stringham JD, Miller D, Flynn HW Jr. Coagulase-negative staphylococcus (CoNS) causing endophthalmitis: a decreasing trend of susceptibility among vancomycin and fluoroquinolones. *Invest Ophthalmol Vis Sci* 2015;56(7):278.
9. Center for Disease Control (CDC) issues recommendations for preventing spread of vancomycin resistance. *Am J Health Syst Pharm* 1995;52(12):1272–1274.
10. Khera M, Pathengay A, Jindal A, et al. Vancomycin-resistant gram-positive bacterial endophthalmitis: epidemiology, treatment options, and outcomes. *J Ophthalmic Inflamm Infect* 2013;3(1):46.
11. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. *Arch Ophthalmol* 2011;129(9):1180–1188.
12. Witkin AJ, Shah AR, Engstrom RE, et al. Postoperative hemorrhagic occlusive retinal vasculitis: expanding the clinical spectrum and possible association with vancomycin. *Ophthalmology* 2015;122(7):1438–1451.
13. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. *Surv Ophthalmol* 2013;58(4):291–310.
14. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115(9):1447–1449.
15. Kessel L, Tendal B, Jorgensen KJ, et al. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology* 2014;121(10):1915–1924.