

Why I Do Not Use Intracameral Antibiotics

The support in the literature is not sufficient in light of the efficacy of topical fourth-generation fluoroquinolones.

BY JOHN R. WITTPENN, JR, MD

Some cataract surgeons use intracameral antibiotics as part of their regimen for preventing endophthalmitis, an infrequent but devastating complication of cataract surgery. A recent, population-based review of 477,627 Medicare claims demonstrated that the incidence of endophthalmitis following cataract surgery rose between 1994 and 2001. The study found a rate of endophthalmitis of 1.79 per 1,000 cases in 1994 and a rate of 2.47 cases per 1,000 in 2001, representing a 37% increase in this 8-year period.¹ Ironically, refinements in surgical technique such as clear corneal incisions that allow for sutureless surgery and rapid visual rehabilitation after phacoemulsification may be at least partially responsible for the increased risk of postoperative infection, including endophthalmitis.²

Today, surgeons use various strategies to decrease the chances of postoperative infection and the vision-threatening complications of endophthalmitis, but the best regimen or approach remains unproven. Among the several current strategies are (1) the perioperative use of topical antibiotics, usually fourth-generation fluoroquinolones, (2) the intracameral injection of antibiotics at the end of the case, and (3) the use of a combination of intracameral and topical antibiotics. Proponents of the intracameral injection of antibiotics during cataract surgery assert that the practice decreases the rate of endophthalmitis, because it helps to eradicate organisms that enter the eye during or immediately after cataract extraction. Several studies, including a recent report from the ESCRS, appear to support this position.³

In my view, however, these recent data do not provide robust support for the superiority of intracameral antibi-

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otics over the perioperative topical antibiotic regimen widely used in the US. First, the ESCRS study did not include in its randomization scheme the use of fourth-generation fluoroquinolones, thus precluding direct comparisons. In addition, the investigators did not address the many risks inherent in the intracameral administration of antibiotics.

THE ESCRS STUDY

The ESCRS study evaluated the effects of intracameral cefuroxime on the rate of postoperative endophthalmitis in 13,698 cataract surgery patients.^{3,4} This partially masked, randomized, multinational study was conducted at 24 sites throughout Europe, with approximately 72 participating ophthalmologists. Patients were randomized to one of four treatment groups: (1) topical placebo preoperatively and immediately after surgery (no intracameral agent); (2) intracameral cefuroxime 1 mg and topical placebo preoperatively and immediately after surgery; (3) perioperative topical levofloxacin 0.5% (two doses preoperatively and three drops immediately postoperatively); and (4) both intracameral cefuroxime and topical levofloxacin (two doses preoperatively and three drops immediately postoperatively). All patients were treated with povidone-iodine 5% pre-

operatively and levofloxacin 0.5% q.i.d. postoperatively for 6 days beginning on the morning after surgery.⁴

In the ESCRS study, the lowest rate of endophthalmitis (0.05%) was seen in patients treated with both intracameral and topical perioperative antibiotics immediately pre- and postoperatively. The highest rate (0.38%) occurred in patients who did not receive any perioperative therapeutic. Topical perioperative antibiotics alone had some effect on the rate of endophthalmitis (0.335% vs 0.380%), but they were not statistically significantly better than the no-treatment group. The topical antibiotic used was levofloxacin, a third-generation fluoroquinolone. In the placebo groups, subjects did not receive the drug until at least 18 hours after surgery.

Patients receiving intracameral cefuroxime with or without topical antibiotics had significantly lower rates of endophthalmitis than those not receiving intracameral dosing ($P=.002$). The rate in both intracameral groups (intracameral only/intracameral with topical pre- and postoperative groups) was 0.073%, whereas the rate in the topical only group was 0.335%. Thus, patients not treated with intracameral cefuroxime had a nearly fivefold greater risk of endophthalmitis than did those who received intracameral dosing.

US STUDY

For comparison, in an evaluation of the two topical fourth-generation fluoroquinolones used in the US to prevent postoperative endophthalmitis, Moshirfar et al⁵ found rates similar to the intracameral group rates reported by Barry et al in the ESCRS study.³ In the retrospective analysis of 20,013 cataract surgeries by Moshirfar,⁵ all patients received either gatifloxacin 0.3% with benzalkonium chloride 0.005% (Zymar; Allergan, Inc, Irvine, CA) or moxifloxacin (Vigamox; Alcon Laboratories, Inc., Fort Worth, TX) every 15 minutes, three times, starting 1 hour before surgery; 16,209 patients received prophylaxis with gatifloxacin and 3,804 patients with moxifloxacin. After surgery, patients used the same fluoroquinolone q.i.d. for 1 week beginning on the day of surgery.

A total of 14 individuals developed endophthalmitis, resulting in an overall rate of 0.07%. The rate of endophthalmitis was 0.06% in the gatifloxacin group and 0.1% in the moxifloxacin group. The difference in the rate of endophthalmitis between the two groups was not statistically significant but favored gatifloxacin.⁵ Of the 14 patients who developed endophthalmitis, six were diagnosed more

TABLE 1. RATES OF ENDOPTHALMITIS

Study	Treatment Group	Rate
ESCRS (13,698 patients) ³ (Note: all patients had 6 days of levofloxacin q.i.d. beginning 18 to 24 hours after surgery)	No intracameral agent, levofloxacin starting after 18 hours only	0.38%
	Intracameral cefuroxime and levofloxacin starting after 18 hours	0.08%
	Levofloxacin pre- and postoperatively	0.29%
	Intracameral cefuroxime and levofloxacin pre- and postoperatively	0.05%
Moshirfar (20,013 surgeries) ⁵ (Note: all patients had the study drug 1 hour before and 1 week after surgery/q.i.d.)	Moxifloxacin	0.10%
	Gatifloxacin	0.06%
	Overall rate	0.07%

than 7 days after surgery. Considering the delayed manifestation of the signs of infection, it is highly unlikely that these infections occurred during the cataract procedure, and intracameral prophylaxis could not have prevented these cases.

Table 1 illustrates the endophthalmitis rates in the studies conducted by the ESCRS³ and Moshirfar.⁵ The incidence of this complication was nearly identical in the gatifloxacin group for Moshirfar and the intracameral cefuroxime/topical levofloxacin perioperative group of the ESCRS study. This similarity suggests that intracameral injection offers little or no benefit over the US regimen of perioperative topical prophylaxis with gatifloxacin. Another interesting comparison may be found in the study by West et al¹ that analyzed records from 1998 to 2001. They showed a rate of endophthalmitis of one in 402 prior to the advent of fourth-generation fluoroquinolones, a lower rate than that seen in the levofloxacin group of the ESCRS study (1:342).

RISK FACTORS FOR ENDOPTHALMITIS

The Moran Eye Center Endophthalmitis Study was conducted to identify risk factors for the development of bacterial endophthalmitis following cataract surgery.⁶ The investigation was based on a retrospective review of 1,525 cataract surgery patients, 27 of whom developed endophthalmitis (approximately 18 of 1,000). The results showed that the timing of the postoperative antibiotic's administration has a dramatic effect on the risk of endophthalmitis (odds ratio: 13.7; $P=.005$). Waiting to instill topical antibiotics until the day after surgery, as was done in the placebo group of the ESCRS study, increased the risk of endophthalmitis nearly 14-fold compared with starting the

antibiotics on the day of surgery, the protocol followed in the study by Moshirfar.

The ESCRS study demonstrated that intracameral dosing has much less impact on the risk of infection than does the timing of antibiotic treatment. This study decreased the risk of endophthalmitis by only fivefold (odds ratio: 4.59; $P=.002$) compared with the topical antibiotic dosing regimen used in the Moran Eye Center Endophthalmitis Study. Thus, although intracameral antibiotics decrease the risk of endophthalmitis, the actual benefit may be less than the ESCRS study suggests if compared with the optimal perioperative use of topical antibiotics (ie, starting fourth-generation topical drops on the day of surgery).

THE BENEFITS AND RISKS OF INTRACAMERAL ANTIBIOTICS

Surgeons considering the use of intracameral antibiotics need to take into account the many potential risks associated with this approach. Perhaps the greatest risk is administering the wrong concentration. Those antibiotics being considered for intracameral use require correct dilution by an experienced pharmacist to avoid potentially toxic effects, such as toxic anterior segment syndrome (TASS). A recent report by the American Society of Ophthalmic Registered Nurses cited intracameral antibiotics that are "improperly dosed, mixed or injected into the eye" as a possible factor in the recent "outbreak" of TASS.⁷

A further issue is the possibly increased risk of macular thickening and cystoid macular edema following cataract surgery using intracameral antibiotics. Although the ESCRS study failed to find any significant change in final visual acuity in the intracameral groups, it did not look closely at macular thickening. My colleagues and I will report a study at this year's ARVO Annual Meeting in which we found that even small changes ($\geq 10 \mu\text{m}$) in macular thickening were associated with a statistically significant decrease in contrast sensitivity. The change may not be sufficient to show alterations in mean visual acuity over large populations of patients, but it may have significant effects on certain patients. The potential of increased macular thickening or cystoid macular edema needs careful evaluation before surgeons transition to the routine use of intracameral antibiotics.

FINAL THOUGHTS

The available data do not support the use of intracameral antibiotics over current perioperative prophylaxis with topical fourth-generation fluoroquinolones. The different protocols used in the ESCRS' and US investigations prevent a direct comparison between treatments. At present, the rates of endophthalmitis with perioperatively dosed topical fourth-generation fluoroquinolones are equivalent to

intracameral treatments but are without the attendant risks of decreased visual function and increased rates of TASS. Also, the duration of protective effect from intracameral antibiotics is short, probably less than 24 hours. Intracameral antibiotics do not address the significant risk of contamination from the surface of the eye that remains until the surgical wound is healed.

Currently, I prescribe Zymar to my patients undergoing cataract surgery, because laboratory and clinical studies have demonstrated the agent's fast killing properties⁸ (also Moss JM, Ta CN, unpublished data to be reported at the ARVO Annual Meeting this year). I instruct patients to begin using the drops 2 days preoperatively and emphasize that they should administer the drug on the day of surgery prior to arriving at the surgery center. They receive Zymar at the conclusion of the cataract procedure and wear a patch and shield for the first 4 postoperative hours.

I recently revised my therapeutic regimen, because six of the 14 cases of endophthalmitis in the study by Moshirfar⁵ occurred more than 7 days after surgery. Upon removal of their eye patch, patients start administering Zymar q2h until bedtime. They continue using the drug q.i.d. for 1 week if the incision is covered by conjunctiva and for 2 weeks if it is a clear corneal incision. ■

John R. Wittpenn, Jr, MD, is a partner in Ophthalmic Consultants of Long Island and is Associate Clinical Professor at the State University of New York in Stony Brook. He is on the speakers bureau for and is a consultant to Allergan, Inc. Dr. Wittpenn may be reached at (631) 941-3363; jr Wittpenn@aol.com.



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