THE QUEST FOR AN OCULAR INJECTABLE ANTIBIOTIC PRODUCT

Skepticism remains in the United States.

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Refreshed interest in the prophylaxis of endophthalmitis via an intracameral (IC) antibiotic injection is perhaps inevitable, spurred by the increasing age and diversity of the patient pool, as well as the rise in resistant ocular bacterial isolates.

Results of the European Society of Cataract & Refractive Surgeons (ESCRS) study,[1] published in 2007, were welcomed in Europe but met with great skepticism in the United States for several reasons. These factors remain the substance of debates, editorials, additional observational studies, and publications to this day. A commercially available IC cefuroxime injection is now approved in 24 European countries, with more than 3 million patients treated, generating ongoing reports that describe clinically meaningful reductions in postoperative endophthalmitis (POE) after instituting IC antibiotic/cefuroxime at the close of cataract surgery. These reports include a key time-trend study from the United States confirming the benefits of adding an IC antibiotic after cataract surgery.[2]

AT A GLANCE

- Ophthalmology in the United States is unfairly handicapped by the lack of an approved ocular antibiotic intracameral injection.
- Although there are myriad variables in antibiotic choices and regimens for ocular surgery, nothing should block the approval of an ocular antibiotic injectable product in this country, especially for patients at increased risk of endophthalmitis who undoubtedly stand to benefit the most.

CRITICISM

An initial criticism levied against the ESCRS study suggested no effect could be attributed to an antibiotic regimen alone, given the large number of confounding variables inherent in cataract surgery and the thousands of patients that would be required to separate these variables.[3] It would seem that the multiplicity of studies now showing reduced POE after an IC antibiotic mitigate against this argument, because more variables could hardly be imagined than are reflected in reports emanating from every corner of the globe. One notable exception is Eastern world regions where microbes reflect different sensitivity patterns than in the United States and where patient colonization patterns and surgical environment also likely differ.[4,5]

To repeat such studies here, in a randomized, controlled, prospective, and masked fashion may not be feasible for many reasons. A close look at the ESCRS methodology (the only prospective, randomized, and partially masked study performed to date) reveals a degree of rigor and standardization, with inclusion of a control group that is unlikely to be reproduced or improved upon elsewhere at this point in time. Among other measures, OR sterility standards at each site were carefully addressed, sites were routinely monitored, and antibiotic drops were packaged in masked fashion and assigned to numbered kits for randomization in a prospective manner—all within a protocol that took 1 year to write and comprised 200 pages. These efforts began more than 15 years ago, and developments in the interim may advocate for newer study designs that address more contemporary questions, in my opinion.

DEBATE

Today, debate continues over several clinical options: IC or topical drops, which antibiotic drops, what regimen of antibiotic drops, no antibiotics at all, "dropless" therapy and surgical technique itself. Each pharmacologic option reflects distinct pharmacokinetic/pharmacodynamic (PK/PD)

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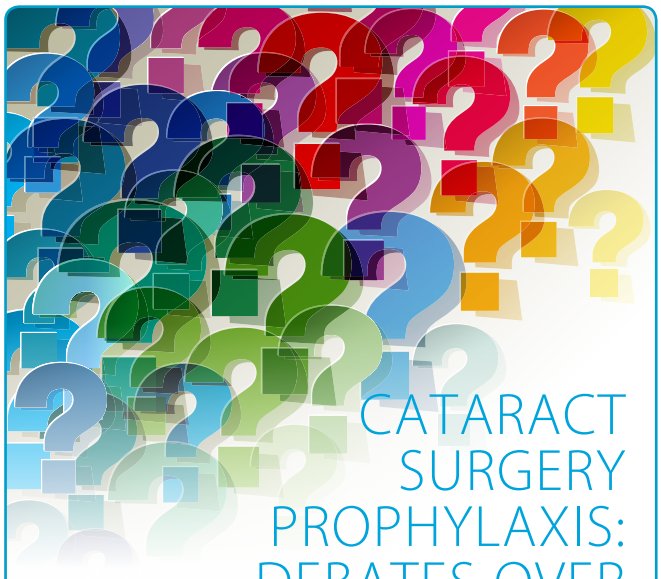
profiles of antimicrobial action that fully underlie the efficacy, or lack thereof, of each regimen within the eye, yet few laboratory studies have been published that adequately explore the fundamental underlying science. Such preliminary studies seem to be a logical next step before subjecting thousands more patients to "cart before the horse" exploration, not to mention the enormous costs of such full-scale, protocol-driven, randomized, masked studies.

With US surgeons already claiming low POE rates near 0.05%, for example, how many patients would be required to show statistical significance with multiple study arms—especially where a true control group is no longer advisable at this stage of the game? If inclusion/exclusion criteria exclude high-risk patients, the differences will be even more difficult to detect. If high-risk patients are included, how will they be evenly distributed in a prospective randomized fashion between study arms, because many risk factors such as posterior capsular rupture, lengthy surgery, complications, and surgeon-related factors are unlikely to be assessed at randomization time? If not randomized, then arms might be imbalanced or require extraordinarily high patient numbers.

WHAT IS MOST PRUDENT?

It would seem prudent to move the needle forward and now include patients known to be at increased risk of POE, because they would benefit most from study findings. In fact, further clinical trials could target these patients specifically. In the hands of prominent surgeons, complications are likely to be minimized and surgical technique perfected, yet this may not reflect all sites or circumstances around the country. How can we identify where these pharmacologic interventions are most useful? How can we separate the need for an intraocular presence of antibiotic versus an external ocular presence of antibiotic? Again, what regimen or combination of regimens is effective?

It seems reasonable to state that, to deliver a drug into the eye, the best method of delivery is into the eye. The number of drugs approved for direct intravitreal injection in recent years, including extended-release intravitreal products, corroborates this fact. These methods are clearly superior to systemic drug delivery where adequate transfer across the blood-eye barrier is not realistic. Topical drops may involve a 100% variability in external tear film concentrations and an approximate 50% variability in aqueous humor penetration. Therefore, if the objective is to deliver high, reliable intraocular antibiotic levels, direct injection is the best option, consistent with other body systems encumbered by unique PK characteristics.



CATARACT SURGERY PROPHYLAXIS: DEBATES OVER CLINICAL OPTIONS

- Which is better, intracameral or topical drops?
- Which antibiotic drops?
- What regimen of antibiotic drops?
- What about no antibiotics at all?
- What about so-called dropless cataract surgery?
- What about surgical technique itself?

Topical drops surely have a place, particularly because the immediate postoperative contribution to POE is not well understood, and because wound healing along with other patient-related factors most likely play a role. The argument that fourth-generation fluoroquinolone drops would have proved superior to third-generation fluoroquinolone drops in the ESCRS study is relatively weak given the lack of evidence that, at the concentrations delivered in drops, this would have made any difference. Furthermore, the pulsed-dose drop delivery used in two study arms was subsequently tested and found to deliver approximately four times higher aqueous humor antibiotic levels than ever reported previously.[6] That dosing regimen—two preoperative drops plus three pulsed drops given 5 minutes apart at the close of cataract surgery—had not, and has not, been duplicated since. It was, however, not statistically comparable to the IC injection. Other important details of the ESCRS study may also not be fully appreciated and have not been tested separately against each opinion or criticism rendered.

Certainly, studies are needed to develop guidelines that set standards of care, but the track for further official approvals of antibiotic products could follow a different course. Drug delivery and antimicrobial action are distinctly separate factors from surgical techniques. In addition, patient-related factors are critical variables in the broad picture. That ophthalmologists will need antibiotics for the eye is understood. That to deliver antibiotics into the eye, we had best deliver them into the eye should also be understood. To continue to protect the ocular surface in the immediate postoperative period is also important and merits further exploration.

MOVING FORWARD

Rather than compare antibiotic drops versus IC injection again, I suggest we recognize the need for approval of both types of products (drops as well as injection) in the specialty of ophthalmology and that we aim further clinical studies toward a better understanding of each surgeon's and patient's particular needs for any given case of ocular surgery. Ophthalmology in the United States is unfairly handicapped by the lack of an approved ocular antibiotic injection, because no available antibiotic of choice is packaged in the much smaller, preservative-free doses required for ocular injection. Such products have certainly been made available for intrathecal use, but US ophthalmologists, faced with a huge clinical need, are forced to rely on extemporaneous compounding and lack access in an emergency.

Many unanswered questions regarding antibiotic time/kill profiles and PK/PD within the eye can first be addressed in simple, scientific ways outside of clinical trials. Whether antibiotic drops, in the levels they deliver over time, are sufficient to kill bacteria inside the eye can easily be studied in preliminary models. Yes, there may be too many variables in ocular surgery to make sweeping statements about one antibiotic or one regimen, but certainly such confusion should not block the approval of an ocular antibiotic injectable product within the United States, especially for patients at increased risk of endophthalmitis who, undoubtedly, stand to benefit the most. ■

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