Anterior Chamber and Vitreous Concordance in Endophthalmitis

Implications for Prophylaxis

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Objective: To examine the relationship between anterior chamber (AC) sterilization and vitreous positivity rate in cases of endophthalmitis.

Design: Retrospective case-control study. A review of all consecutive cases of endophthalmitis (N=758) between January 1, 1999, and December 31, 2008, identified 229 matched AC and vitreous samples. Matched samples were evaluated for sensitivity and specificity, positive and negative predictive values, and positive and negative likelihood ratios. The main outcome measures were sensitivity and specificity of AC and vitreous samples in cases of endophthalmitis. Antibiotic resistance profiles from culture-positive endophthalmitis cases are given.

Results: Gram-positive organisms accounted for 124 of 154 (80.5%) culture-positive endophthalmitis isolates (146 of 229 [63.8%]). The sensitivity (0.36%) and specificity (0.71%) of AC culture results were poor predictors of positive vitreous culture. Positive and negative predictive values were less than 60%. Positive likelihood ratio (1.24) and negative likelihood (0.91) of AC culture results did not aid in predicting vitreous findings. Gram-positive isolates demonstrated in vitro resistance to moxifloxacin (47.1%), ciprofloxacin (43.4%), gatifloxacin (36.8%), levofloxacin (29.0%), gentamicin (19.2%), and ceftazidime (16.7%).

Conclusions: The AC lacks concordance with vitreous findings in cases of endophthalmitis. Use of broad-spectrum antibiotics to sterilize the ocular surface and provide therapeutic levels in the AC may not prevent endophthalmitis. In this study, the finding of a sterile AC did not rule out vitreous infection. These results may have implications for the routine use of broad-spectrum antibiotics as a means of vitreous protection and endophthalmitis prophylaxis.

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ENDOPHTHALMITIS IS A SERIOUS and potentially vision-threatening intraocular infection. Exogenous (eg, postoperative, traumatic, and postintravitreous injection) and endogenous (eg, liver abscess, pneumonia, and endocarditis) forms of endophthalmitis manifest as progressive vitritis or panuveitis and require urgent evaluation and management. The Endophthalmitis Vitrectomy Study[1] remains the benchmark for the treatment of endophthalmitis and specifies the roles of immediate pars plana vitrectomy (light perception–only visual acuity at initial examination) vs vitreous tap and antibiotic injection and revealed that intravenous antibiotics were not of benefit in the treatment of postsurgical endophthalmitis. Routine use of topical broad-spectrum antibiotics to reduce ocular surface microflora and to provide therapeutic drug levels in the anterior chamber (AC) for vitreous prophylaxis before cataract and other anterior segment surgical procedures is a common but increasingly debated issue.[2-4]

Cataract surgery is the most frequently performed intraocular surgery. The incidence rate of acute endophthalmitis following cataract surgery ranges from 0.08% to 0.68%.[4-10] In cataract surgery, the use of fluoroquinolones as perioperative topical broad-spectrum antibiotic eyedrops is considered of benefit in preventing endophthalmitis because of favorable AC penetration and increased efficacy against gram-positive bacteria.[11-15] The protective and therapeutic effect may be a combination of resident skin flora sterilization and elimination of microbes that might enter the AC during surgery. The relationship between a sterile anterior segment or high intracameral antibiotic levels and the prevention of microbial invasion of the vitreous remains unclear.[2,3]

In a 2007 study,[10] intracameral cefuroxime was shown to reduce the risk of endophthalmitis following cataract surgery in one large multicenter study. The use of levofloxacin (0.5%) eyedrops preoperatively was not found to reduce the risk of endophthalmitis.[10] However, debate about the efficacy and safety of intracameral antibiotics for the prevention of post–cataract surgery endophthalmitis remains controversial.[16-19] Povidone iodine remains the only other agent that has been shown to provide a protective effect against the development of endophthalmitis.[20]

The purpose of this study was to examine the relationship between AC sterilization and vitreous positivity rate in cases of endophthalmitis. Between January 1, 1999, and December 31, 2008, endophthalmitis cases with both AC and vitreous microbiologic culture results were examined to determine the concordance between AC and vitreous results and the emergence of in vitro resistance to a select group of antibiotics. Given the controversy about topical vs intracameral antibiotics in endophthalmitis prophylaxis, alongside the increasing rates of cataract surgery and intravitreous injections, such a comparison might help in the debate on the value of AC sterilization and its effect on vitreous culture results, as well as endophthalmitis prophylaxis by extrapolation.

METHODS

We retrospectively reviewed all consecutive cases of endophthalmitis (endogenous and exogenous) (N=758) submitted for microbiologic culture at the Bascom Palmer Eye Institute, Miami, Florida, between January 1, 1999, and December 31, 2008. From this group, we identified 229 matched AC and vitreous samples, which were evaluated for sensitivity and specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios. Analysis of AC and vitreous by means of a 2×2 diagnostic accuracy table was performed to determine the relationship between AC sterilization and vitreous positivity rate. The AC results were defined by the diagnostic test in question, and the vitreous results served as the gold standard.

Antibiotic susceptibility profiles of culture-positive endophthalmitis isolates (n=146) were reviewed. Trends were assessed for in vitro resistance to vancomycin, gentamicin, ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. The study fully adhered to the Declaration of Helsinki and all federal and state laws.

RESULTS

A significant difference existed between the culture-positive rates for AC (74 of 229 [32.3%]) and vitreous (112 of 229 [48.9%]) ($\chi^2=13.07$, $P<.001$). The overall culture-positive rate was 146 of 229 matched study cases (63.8%). In 40 cases, both AC and vitreous identified the same isolate, and these were defined as true-positive results. In 64 cases, AC identified no isolates, but vitreous was positive; in 8 cases, AC and vitreous identified different microorganisms. Together, these 72 cases represent the false-negative group (**Table 1**). False-positive results included 34 cases in which AC was positive for microorganisms but vitreous revealed no isolates. Finally, 83 cases were negative for both AC and vitreous and correspond to the true-negative group.

Table 1. Summary of 229 Endophthalmitis Cases Between 1999 and 2008

Anterior Chamber Diagnostic Test Result	Vitreous Isolate Result (Gold Standard)	
	Positive	Negative
Positive	40 True positives	34 False positives
Negative	72 False negatives[a]	83 True negatives
Total	**112**	**117**

[a] Eight matched cases cultured different microorganisms from anterior chamber vs vitreous and are included as false-negative results because of the lack of concordance between anterior chamber and vitreous samples.

The AC culture results poorly detected vitreous isolates, with a sensitivity of 36% (Table 1). Similarly, AC culture was inadequate at predicting negative vitreous culture results, with a specificity of 71%. The PPV and NPV were 54% and lacked usefulness in interpreting AC and vitreous microbiologic results. The positive and negative likelihood ratios for AC were 1.24 and 0.91, respectively, indicating that AC results did not aid in predicting vitreous findings in any meaningful way. General concordance between AC and vitreous cultures was 53.7% (123 of 229).

A total of 154 microorganisms were identified from 146 culture-positive endophthalmitis cases (**Table 2**). Gram-positive organisms accounted for 80.5% (124 of 154) of isolates, and the most prevalent included *Staphylococcus epidermidis* (29.2%), *Streptococcus* species (18.2%), and coagulase-negative *Staphylococcus* species (11.7%). Gram-negative microorganisms represented 11.0% of isolates (17 of 154); 82.4% (14 of 17) of these were *Pseudomonas aeruginosa*. Yeast and fungi composed 8.4% (13 of 154) of isolates, with *Candida* species being the most common ([30.8%] 4 of 13).

Gram-positive organisms demonstrated significant antibiotic resistance to the second-generation fluoroquinolone ciprofloxacin (43.4%), third-generation levofloxacin (29.0%), and fourth-generation moxifloxacin (47.1%) and gatifloxacin (36.8%), as well as gentamicin (19.2%) and ceftazidime (16.7%) (Table 2). All gram-positive microorganisms were sensitive to vancomycin. Gram-negative isolates showed antibiotic resistance to gentamicin (23.1%) but were 100% sensitive to ciprofloxacin and levofloxacin.

COMMENT

In this retrospective study, there was a lack of concordance between culture positivity and spectrum of isolates among matched AC and vitreous cultures. The AC lacked high sensitivity; therefore, a negative test result could not be used to rule out vitreous infection. Similarly, AC results lacked high specificity, and a positive test result could not be used to rule in vitreous infection. Together, AC and vitreous displayed poor concordance, and AC results were in no way helpful at indicating or predicting vitreous positivity or negativity rates. Our calculated PPV and NPV, both of which fell below 60%, demonstrated that AC culture results for this popu-

Table 2. Antibiotic Resistance Profiles of Gram-positive and Gram-negative Bacterial Isolates Among 141 Culture-Positive Endophthalmitis Cases Between 1999 and 2008[a]

Resistant Isolates[b]	No. of Cases/Total No. of Cases (%)					
	Vancomycin	Gentamicin	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
124 Gram-positive[c]	0/97 (0)	14/73 (19.2)	33/76 (43.4)	18/62 (29.0)	7/19 (36.8)	8/17 (47.1)
17 Gram-negative	NT	3/13 (23.1)	0/13 (0)	0/10 (0)	NT	NT

Abbreviation: NT, not tested.
[a] Eight matched cases cultured different microorganisms from anterior chamber vs vitreous; therefore, the total number of microorganisms identified is 154.
[b] The remaining 13 isolates are fungi; antibiotic sensitivities were not performed on fungal isolates.
[c] In addition to those listed in the text, prevalent gram-positive organisms included methicillin-sensitive *Staphylococcus aureus* (8 of 154 [5.2%]), methicillin-resistant *Staphylococcus aureus* (4 of 154 [2.6%]), and *Propionibacterium acnes* (8 of 154 [5.2%]).

lation were not useful in predicting microbial invasion or contamination of the vitreous chamber.

Predictive values were used to ascertain the probability of vitreous outcomes given a positive or negative AC result. The PPV and NPV are dependent on the disease prevalence and the target population. The prevalence of culture-proven endophthalmitis among this population was 48.9%. Therefore, similar to the sensitivity and specificity results, the low PPV and NPV in this study showed AC culture status to be a poor predictor of vitreous results. Unlike predictive values, likelihood ratios are independent of disease prevalence.[21] The positive likelihood ratio herein revealed a minimal increase in the likelihood of AC and vitreous congruency. Furthermore, the negative likelihood ratio confirmed an insignificant decrease in the likelihood of vitreous outcomes given AC results. These results are surprising because a common inference is that AC status is, at least partly, congruent with vitreous status and include therapeutic AC antibiotic levels that afford vitreous protection from microbial invasion. Instead, our results demonstrated that AC status has a negative correlation with vitreous results.

Results of matched AC and vitreous samples (N=21) from the European Society of Cataract & Refractive Surgeons multicenter study[22] on prophylaxis of postoperative endophthalmitis confirmed the insensitivity of AC culture results in predicting vitreous culture outcomes. General agreement between AC and vitreous cultures in this population was 76.2%, with sensitivity and specificity of 60% and 91%, respectively. Both PPV (85.7%) and NPV (71.4%) were less than 90%. As in our study, likelihood ratios confirmed the inadequacy of AC culture status to provide relevant information about vitreous culture positivity. The Endophthalmitis Vitrectomy Study[23] confirmed a significant difference in culture-positive rates between AC and vitreous samples. Among 323 laboratory-confirmed cases, culture-positive rates were 48.9% (158 of 323) for AC and 87.3% (282 of 323) for vitreous samples ($P<.001$). These results draw into question the current approach of targeting AC for endophthalmitis prophylaxis.

Fluoroquinolone resistance among 229 matched cases in this study was greater than 20% for all classes. These results confirm previous data from our and other centers about growing in vitro resistance to older and newer fluoroquinolones.[24-28] Coupled with the increasing reports of clinical failure with this class of antibiotics, the continued use of these antibiotics for prophylaxis and treatment of endophthalmitis may need to be revisited.[29-31] Current debate about the use of intracameral cefuroxime for the prevention of endophthalmitis needs additional study. Among 11 isolates available for in vitro evaluation among patients with presumed endophthalmitis in the European Society of Cataract & Refractive Surgeons study,[22] documented resistance was 45.5% (5 of 11) for cefuroxime and 27.3% (3 of 11) for levofloxacin.

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