

The articles that follow are part of an ongoing series that aims to review collaborative prospective studies supported by the National Eye Institute. The first article, written by investigators, will remind readers of the rationale, goals, methods, findings, and recommendations. The second article, written by an expert who did not participate in the investigations, will offer a constructive critique and attempt to estimate the impact of the study on the practice of ophthalmology.

Treatment of Postcataract Extraction Endophthalmitis

A Summary of the Results From the Endophthalmitis Vitrectomy Study

Bernard H. Doft, MD

IN THE LATE 1980S, THE VALUE OF PARS PLANA VITRECTOMY (VIT) in the initial management of postcataract extraction-related endophthalmitis was unclear. Immediate VIT offered several theoretical advantages, but limited data from human case series had not shown that VIT conferred an advantage. In those reports, VIT had been reserved for eyes with the worst clinical manifestation. Because of severe selection bias in the reports, the role of pars plana VIT in the management of patients with endophthalmitis after cataract surgery remained uncertain.

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While it was known that even the newer drugs given systemically did not reach sufficient intraocular concentrations to be effective against many common bacteria, most physicians were still administering intravenous antibiotics for postcataract-related endophthalmitis. In addition to the question of limited efficacy, their use added the risk of systemic toxicity and additional expense. While intravitreal injection of antimicrobial agents had become common for endophthalmitis, physicians were hesitant to omit systemic drugs from the treatment regimen for fear that if they were of value their patients would be deprived of benefit and for fear of the medicolegal consequences of not using what was then considered the standard of care.

The Endophthalmitis Vitrectomy Study (EVS) was born to address these issues. A randomized, multicenter, clinical trial supported by the National Eye Institute, it was designed to determine the role of immediate pars plana VIT and, separately, the role of systemic antibiotics in the management of endophthalmitis after cataract extraction or secondary intraocular lens insertion.

STUDY DESIGN

Patients were eligible for the EVS if they had clinical signs and symptoms of bacterial endophthalmitis within 6 weeks of cataract surgery or secondary lens implanta-

tion. Eligibility required a visual acuity of light perception (LP) or better and worse than 36 letters at 4 m (approximately 20/50 or worse) on the Early Treatment Diabetic Retinopathy Study visual acuity chart, sufficient clarity of the cornea to potentially perform pars plana VIT, and the presence of either a hypopyon or sufficient clouding of the anterior chamber or vitreous to obscure a view of second-order retinal arterioles.

Patients were excluded if they had known eye disease limiting visual acuity to 20/100 or worse before development of cataract and for other potentially confounding conditions described in more detail elsewhere.¹ Of 855 screened patients with endophthalmitis within 6 weeks after cataract extraction or a secondary lens implant, 510 met the eligibility criteria and 420 were enrolled at 1 of 24 study centers.

Patients were randomized to undergo either an immediate pars plana VIT (n=218) or tap/biopsy (TAP) (n=202) of the vitreous. All patients were also randomly assigned to either receive intravenous (IV) antibiotics (n=206) or not receive them NOIV (n=214). Except for these random treatment assignments, all patients were provided the same treatment regimen.

Treatment was initiated within 6 hours of when patients were initially seen. Patients assigned to VIT underwent a 3-port pars plana VIT. Patients assigned to TAP had a vitreous specimen collected either by a trans pars plana vitreous aspiration with a needle or by a vitreous biopsy through a single sclerotomy with vitrectomy instrument. With TAP, the vitreous sample was less than 0.3 mL.

At the end of the initial procedure, all patients received intravitreal amikacin, 0.4 mg, and vancomycin, 1.0 mg. In developing the protocol, EVS investigators had to determine which drugs to use for intravitreal administration. It was clear that vancomycin needed to be one of the choices. For the other choice, there was controversy between using amikacin and ceftazidime. Amikacin had a small (believed to be <0.5%) risk of macular infarction and ceftazidime did not. However, it was believed that this small risk was acceptable in view of certain potential benefits of amikacin over ceftazidime. The fact that amikacin demonstrated synergy with vancomycin in killing gram-positive organisms, such as entero-

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cocci, other streptococci, and staphylococci, was important. It provided both concentration-dependent killing and less susceptibility to inoculum effect compared with ceftazidime.² Furthermore, although not known at the time, it was subsequently determined that ceftazidime may precipitate (and, therefore, be less bioavailable) when used with vancomycin in the vitreous.³

In addition to intravitreal antibiotics, all patients received vancomycin, 25 mg; ceftazidime, 100 mg; and dexamethasone, 6 mg, subconjunctivally. Topical antibiotics, cycloplegic agents, and corticosteroids were used, as was oral prednisone, for the first 5 days.

Patients randomized to IV antibiotics received ceftazidime and amikacin at appropriate systemic doses for 5 to 10 days. Patients randomized to the NOIV group did not receive systemic antimicrobial agents. For the IV antibiotics group, the rationale for not using vancomycin systemically had been questioned and addressed.⁴⁻⁷ The most important reason that vancomycin was not used systemically was that it has negligible intravitreal penetration after systemic administration. Furthermore, the vancomycin already given by direct intravitreal injection has a long intravitreal half-life. The minimal contribution to the amount of antibiotic in the vitreous that systemic vancomycin would provide would be trivial compared with the 50 µg/mL still present in the vitreous (even in eyes that underwent VIT) as long as 4 days after intravitreal injection.⁷

OUTCOME ASSESSMENT

The primary study outcomes were visual acuity as determined by a masked observer and assessment of media clarity. Assessment was performed at 3 months and at the final study follow-up, which occurred between 9 and 12 months after enrollment. At the 9-month examination, patients who had further potentially remediable ocular problems were allowed to have additional procedures as required, in which case the final study visit occurred at 12 months.

RESULTS

The median age was 75 years, and 57% of the patients were women. The median interval from cataract extraction or secondary lens implantation to initial examination at a study center was 6 days. The most common symptom was blurred vision. Pain was absent in one-quarter of patients. At initial examination, about 90% of patients had an acuity of worse than 5/200. Of the patients, 26% had visual acuities no better than LP. The media clarity at initial examination was such that in 80% of patients no retinal vessels could be seen with indirect ophthalmoscopy.

Cultures showed no growth of any organism in 18% of patients, equivocal growth in 13%, and confirmed growth in 69%. Of the 291 patients who showed confirmed growth, 68% showed gram-positive coagulase-negative organisms, 22% showed other gram-positive organisms, such as *Streptococcus* and *Staphylococcus aureus*, 6% showed gram-negative organisms and 4% had multiple organisms.

Media cleared more quickly after VIT than after TAP. At the 3-month follow-up, a "20/40" view of the retina

by indirect ophthalmoscopy was found in 86% of eyes that underwent VIT but only in 75% of eyes that underwent TAP ($P = .004$). At the final study follow-up, 85% of all patients had this level of media clarity, with no significant difference ($P > .05$) by treatment allocation. There was also no difference in media clarity based on systemic IV or no IV antibiotic assignment.

Overall visual outcomes in the EVS were excellent, with 53% of all patients achieving a visual acuity of 20/40 or better and 74% achieving a visual acuity of 20/100 or better. Only 11% had final visual acuities worse than 5/200, and this included 5% with no LP.

The benefit of VIT in the treatment of endophthalmitis was strong, but its benefit was limited to a specific subgroup of patients. Patients who had LP-only visual acuity on initial examination and who underwent immediate VIT had a 3 times better chance of achieving a 20/40 visual acuity (33% vs 11%), almost double the chance of achieving a 20/100 final visual acuity (56% vs 30%), and less than half the risk of severe visual loss to less than 5/200 (20% vs 47%). The differences were significant ($P < .001$). Therefore, the findings of the EVS strongly support the use of immediate VIT in patients in whom endophthalmitis develops after cataract extraction, who have LP-only visual acuity at initial examination, and who meet EVS enrollment criteria.

Patients who were seen with better than LP visual acuity (ie, hand motions or better) at initial examination had a similar chance of achieving 20/40 or better acuity (66% vs 62%) and 20/100 or better acuity (86% vs 84%) and a similar risk of visual loss to worse than 5/200 (5% vs 3%) regardless of whether they underwent VIT or TAP. Because patients who were seen with a visual acuity of better than LP at initial examination did just as well with immediate VIT as they did with TAP, there was generally no advantage to routinely performing immediate VIT in this group.

What about the effect of systemic antibiotics? The results showed no statistically significant difference ($P > .05$) in visual outcome by whether patients received systemic antibiotics. This held for all subgroups.

About 14% of the EVS population was diabetic. The EVS was not designed to address differences based on the presence or absence of diabetes mellitus, but an exploratory analysis was performed at the conclusion of the study. The number of patients with diabetes mellitus was small ($n = 36$) and, while the differences between diabetic and nondiabetic patients were not statistically significant, interesting trends did exist.⁸ Diabetic patients in the EVS had worse outcomes than nondiabetic patients. A visual acuity of 20/40 was obtained in 39% of diabetic patients vs 55% of nondiabetic patients. A visual acuity of worse than 5/200 occurred in 20% of diabetic patients vs 10% of nondiabetic patients. Diabetic and nondiabetic patients who had LP visual acuity at initial examination did better with VIT than with TAP. However, unlike nondiabetic patients, diabetic patients who had better than LP visual acuity at initial examination did seem to benefit with VIT because 57% of diabetic patients who underwent VIT achieved 20/40 visual acuity compared with 40% of those who underwent TAP.

CONCLUSIONS

The findings of the EVS strongly support the use of immediate VIT in eyes with endophthalmitis after cataract extraction or secondary lens implantation in which the visual acuity is LP only at initial examination and in which the EVS enrollment criteria are met. However, study patients who had a visual acuity of hand motions or better at initial examination did just as well with immediate VIT as with TAP. Therefore, there is no advantage to routinely performing immediate VIT in patients who had better than LP visual acuity when first seen. (A possible exception exists for diabetic patients who have a visual acuity of better than LP when first seen *vide supra* [see the last paragraph in the "Results" section].)

An important study finding was that there was no difference in visual acuity or media clarity outcome whether systemic antibiotics were used. In the past, the use of intravenous antibiotics had been part of the standard of care in the management of postsurgical endophthalmitis. Systemically administered antibiotics may have serious systemic adverse effects, their use is expensive, and, for intravenous drugs, administration generally requires hospitalization. Thus, the finding that systemic antibiotics did not provide benefit may save patients from toxicity risk and may allow patients to be discharged from the hospital earlier or, in some cases, not be hospitalized at all. The EVS findings support omitting systemic antibiotics in the management of acute endophthalmitis that occurs within 6 weeks of cataract surgery.

While, strictly speaking, the findings regarding intravenous antibiotics apply only to the drugs used in the study, it is not unreasonable to extrapolate to other drugs. The amount of antimicrobial agent that is delivered to the vitreous cavity is so great with intravitreal injection compared with the amount that can enter this cavity from systemic administration that systemically administered drugs are not likely to provide additional immediate benefit over intravitreal drugs alone, no matter what the drug. Furthermore, intravitreal drugs get to the site immediately, whereas systemically administered drugs do not.

Finally, EVS results apply to postcataract extraction endophthalmitis. They do not necessarily apply to other types of endophthalmitis, such as endogenous endophthalmitis or bleb- or trauma-induced endophthalmitis.

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Additional Information: Dr Doft is chair of the EVS, which is a registered clinical trial. Trial registration: <http://clinicaltrials.gov/show/NCT00000130>.

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From the Archives of the Archives

In 1938, the work of Bucklers and his associate Gilch resulted in an orderly classification of the corneal dystrophies. In an investigation undertaken for the German government, under the sterilization of the unfit order, these workers carefully examined 12 family groups, consisting of 800 individuals, living in 35 small communities in Wuerttemberg. Among them were a total of 129 patients suffering from some type of corneal dystrophy.

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