Diabetes and Postoperative Endophthalmitis in the Endophthalmitis Vitrectomy Study

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Objectives: To determine whether there was a different response to vitrectomy and tap/biopsy with or without systemic antibiotic treatment in the Endophthalmitis Vitrectomy Study and whether the signs and symptoms of endophthalmitis differ between diabetic and nondiabetic patients.

Design: A multicenter clinical trial in which patients with acute post–cataract extraction endophthalmitis were randomly assigned in a 2 × 2 factorial design to vitrectomy or tap/biopsy, in each case with or without intravenous antibiotics, and followed up for 9 months. Outcome measures included visual acuity assessed in standardized fashion.

Results: Fifty-eight of 420 study patients had diabetes. Diabetic patients had slightly worse vision and ocular media at the baseline assessment. Only 39% of diabetic patients compared with 55% of nondiabetic patients achieved 20/40 final vision. Both diabetic and nondiabetic patients with initial light perception (LP)-only vision had better visual results with immediate vitrectomy. For those with better than LP baseline vision, patients with diabetes achieved visual acuity of 20/40 more often with vitrectomy (57%) than with tap/biopsy (40%), but this difference was not statistically significant. Patients without diabetes did equally well with vitrectomy or tap/biopsy.

Conclusions: For patients with better than LP vision, tap/biopsy is appropriate for those without diabetes. A clinical trial of a sufficient number of diabetic patients with better than LP vision is necessary to determine the best management for this group. At present, initial vitrectomy or tap/biopsy are reasonable approaches for diabetic patients with better than LP vision.


Most, but not all, literature suggests that persons with diabetes are at increased risk of developing endophthalmitis after intraocular surgery.1-4 In previous reports,2 14% to 21% of patients with endophthalmitis were diabetic. Diabetic patients who develop endophthalmitis after cataract extraction tend to have worse visual results than nondiabetic patients. The worse visual results may occur more commonly among diabetic patients with diabetic retinopathy compared with those who do not have diabetic retinopathy.3

The Endophthalmitis Vitrectomy Study (EVS)7 was a multicenter clinical trial sponsored by the National Eye Institute to compare immediate pars plana vitrectomy and tap/biopsy, and to compare the use vs nonuse of systemic (intravenous [IV]) antibiotics for the treatment of postoperative bacterial endophthalmitis. Patients were assigned by random allocation according to a 2 × 2 factorial design to 1 of 4 groups: vitrectomy with IV antibiotics, tap/biopsy with IV antibiotics, vitrectomy without IV antibiotics, and tap/biopsy without IV antibiotics. The EVS showed that systemic antibiotics did not provide benefit in the management of acute post–cataract extraction endophthalmitis. The study also showed that for the entire group of EVS patients, those who had light perception (LP)-only vision at the baseline assessment had better final visual results if they underwent an immediate pars plana vitrectomy, but those with better than LP vision at baseline did not obtain additional benefit with immediate vitrectomy.7 Of the 420 patients enrolled in the EVS, 58 had diabetes. This article presents EVS results for the subset of patients who were diabetic.
PATIENTS AND METHODS

THE EVS TRIAL

The methods and results of the EVS have been reported elsewhere. Briefly, patients with suspected bacterial endophthalmitis after cataract surgery or secondary lens implantation were screened for eligibility at 24 clinical sites in the United States. Between February 1990 and January 1994, 420 subjects met the inclusion and exclusion criteria and consented to participate in the trial.

These patients were randomly assigned according to a $2 \times 2$ factorial design to 1 of 4 treatment groups: initial vitrectomy with IV antibiotics, initial vitrectomy without IV antibiotics, initial tap/biopsy with IV antibiotics, and initial tap/biopsy without IV antibiotics. The details of the surgical procedures and the use of the IV antibiotics are presented elsewhere.

All patients had standard visual acuity assessments based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol at entry and at 3- and 9-month follow-up visits. An additional assessment was made at a 12-month visit for patients who had additional procedures, based on the examination results of the 9-month visit. Best-corrected visual acuity was measured after manifest refraction using the ETDRS visual acuity charts. According to protocol, 3 thresholds of visual outcomes were chosen to reflect different levels of functional vision: 20/40 (70 letters) or better, 20/100 (50 letters) or better, and 5/200 (5 letters) or better.

DATA COLLECTION

At the initial visit, the data collected consisted of patient-specific history (e.g., age and sex), history of the involved eye (e.g., previous glaucoma treatment and history of retinal detachment), current antibiotic use, and a clinical examination of the involved eye. The presence of diabetes was defined by a patient taking any medication for glycemic control.

The cataract surgical wound was examined to determine the presence or absence of a wound dehiscence, a wound leak, or a vitreous wick and whether the wound margin was fully covered by conjunctiva. The presence of an intraocular lens and its type were noted. The capsule was assessed to determine if it was present, intact, or not intact. Indirect ophthalmoscopy was performed to assess the red reflex and, to the extent possible, obtain an overall stereoscopic view of the fundus and vitreous, including the posterior pole and an anterior view that extends as far to the periphery as possible. A B-scan ultrasound was performed to determine if a choroidal detachment and/or a retinal detachment was present when the ocular media prevented evaluation of the choroid or retina.

During the initial surgical procedure (vitrectomy or tap/biopsy), anterior chamber and vitreous specimens were obtained and inoculated in culture media as described previously. Each microbiologic isolate was assigned a “laboratory infection status” category based on a definition that integrated the culture and Gram stain results from the patient’s eye. The 4 categories of laboratory infection status were (1) no or equivocal only growth, (2) Gram-positive coagulase-negative growth, (3) other Gram-positive growth, and (4) Gram-negative growth.

If there were complications during the initial procedure, the information regarding the type of complication was recorded. The study protocol allowed for clinically appropriate additional procedures to take place at any time during the course of follow-up.

STATISTICAL METHODS

The distribution of baseline characteristics, microbiology spectrum, and complications were compared among those with and those without a history of diabetes using a chi-squared test for discrete data and a Wilcoxon rank sum test for continuous data. For those visual acuity thresholds, dichotomous outcome differences among those with and those without diabetes were presented.

To examine the full range of visual acuity outcomes, we considered the visual acuity score based on the ETDRS acuity chart. Outcomes are reported for 396 of the 420 EVS patients who completed a final follow-up visit. Among the 396 patients were 2 for whom final visual acuity data were missing, resulting in final visual acuity being reported for 394 patients. (Of the 40 patients with better than LP vision and diabetes at the baseline assessment, 4 had missing data for the final follow-up assessment. The initial treatment assignments for these 4 patients were: 1 each to vitrectomy with IV, vitrectomy without IV, tap/biopsy with IV, and tap/biopsy without IV. These missing data were balanced across the treatment groups.) The visual acuity scores among EVS patients were not normally distributed, so linear models that require an assumption of normality were not appropriate. A Mantel-Haenszel log-rank analysis was used with each visual acuity score as a stratum. This allowed outcome comparisons of the proportion of patients with visual acuity scores of more than 1 letter, more than 2 letters, more than 3 letters, and so on. This analysis of outcomes is parallel to the use of life-table analysis. A figure was constructed to present the cumulative proportion of patients according to the final visual acuity score achieved. The figure is parallel to usual “survival curves.” A log-rank statistic was used to compare the distributions between diabetic and nondiabetic patients after verifying the assumption of proportional hazards; a stepwise Cox regression model was used to extend analysis of visual acuity outcome to take into account baseline characteristics.

RESULTS

BASELINE CHARACTERISTICS

Fifty-eight (13.8%) of the 420 EVS patients had diabetes. Table 1 describes the baseline characteristics. In general, diabetic patients with endophthalmitis were similar to nondiabetic patients with endophthalmitis, although there was a significantly higher percentage of non-whites and patients with a history of hypertension in the diabetic group. There was no difference in the distribution of the symptoms of endophthalmitis (red eye, pain, blurred vision, swollen lid) between the 2 groups. There was a trend for poorer vision (74.1% with either LP only or hand motions only in the group with diabetes vs 69.6% in the group without diabetes), but this difference was
not statistically significant. Similarly, those with diabetes tended to have worse media clarity at the initial visit. For diabetic patients, there was no view of a retinal vessel in 89.7% compared with 77.4% for nondiabetic patients (P = .09).

There was a significant difference in the presence of rubeosis iridis, with 8.6% of the eyes of diabetic patients having rubeosis iridis compared with 1.9% of the eyes of nondiabetic patients (P = .004). While the proportion of those having a hypopyon (89.7% for those with diabetes vs 89.1% for those without diabetes; P = .36) was similar, there was a significant difference in the median size of the hypopyon. In patients with a hypopyon, those with diabetes had a 50% larger hypopyon (median, 1.5 mm for diabetic vs 1.0 mm for nondiabetic; P = .03).

The mean time from the inciting surgery until development of ocular symptoms was 6 days (median, +) in the diabetic group and 7 days (median, +) in the nondiabetic group. This difference was not statistically significant.

### MICROBIOLOGY SPECTRUM BY DIABETES STATUS

The microbiology spectrum by diabetes status is presented in Table 2. There was a significant difference in the distribution of the microbiology results between those with and those without diabetes (P = .046). The nondiabetic group was twice (33.2%) as likely to have no
growth than the diabetic group (15.5%). Conversely, the diabetic group was more likely to show confirmed growth than the nondiabetic group. Gram-positive, coagulase-negative micrococci were significantly more likely to grow from the eyes of diabetic patients (45.0%) than from eyes of nondiabetic patients (38.6%) from eyes of nondiabetic patients (45.0%). Cultures of diabetic patients were only slightly more likely to yield virulent organisms (other Gram positive and Gram negative): 25.9% of the initial 58 diabetic patients, 2 from the vitrectomy group and 2 from the tap/biopsy group. For all of the visual acuity thresholds tested, the diabetes group had a significantly higher proportion with poor vision (<5/200, 5 letters: 20.4% vs 10.0%; <20/100, 50 letters: 44.4% vs 22.7%; <20/40, 70 letters: 61.1% vs 44.7%). Conversely, the nondiabetic group had more patients achieve good vision, with 53.3% achieving 20/40 vision compared with 38.9% of diabetic patients.

### COMPLICATIONS AND ADDITIONAL PROCEDURES

Table 3 shows that there was no significant difference in the distribution of operative complications during the initial procedure between those with and those without diabetes (1.7% vs 5.0%; *P* = .27). There was also no difference in the rate of retinal detachment at any time during follow-up between the 2 groups (diabetics vs nondiabetics, 6.9% vs 8.6%; *P* = .67).

Diabetic patients were somewhat more likely to have an additional procedure during the course of the follow-up (diabetics vs nondiabetics, 43.1% vs 34.0%; *P* = .18). This difference was most marked for early additional procedures (performed within the first week after the initial assessment) with 20.7% of diabetic patients undergoing an early additional procedure compared with 8.8% of nondiabetic patients (*P* = .006). There was only a little difference in late additional procedures, with 31.0% incidence among diabetics vs 27.1% in nondiabetics.

### VISUAL OUTCOME

Table 4 presents the visual outcome results for the 394 patients with and without diabetes for whom these data are available. Final acuity data were not available for 4 of the initial 58 diabetic patients, 2 from the vitrectomy group and 2 from the tap/biopsy group. For all of the visual acuity thresholds tested, the diabetes group had a significantly higher proportion with poor vision (<5/200, 5 letters: 20.4% vs 10.0%; <20/100, 50 letters: 44.4% vs 22.7%; <20/40, 70 letters: 61.1% vs 44.7%). Conversely, the nondiabetic group had more patients achieve good vision, with 53.3% achieving 20/40 vision compared with 38.9% of diabetic patients.

The Figure shows the cumulative percentage distribution of final visual acuity scores in both groups. Note that a lower percentage of diabetic compared with nondiabetic patients reach a given visual acuity threshold throughout the entire acuity range. For example, 56% of patients with diabetes reach the 20/100 (50 letter) threshold compared with 77% of those without diabetes.
Because the baseline characteristics associated with poor visual outcome were often interrelated, independent risk factors were determined, ie, factors related to outcome even after their association with other factors was taken into consideration. Table 5 presents the relative risks for significant independent baseline factors (based on a Cox regression analysis) for a decrease over the entire range of visual acuity (as distinct from individual visual acuity thresholds).7 After controlling for the other factors associated with final visual acuity score (eg, age and baseline visual acuity), patients with diabetes had a 1.55 risk of decreased final vision compared with those without diabetes.

**TREATMENT INTERACTION WITH DIABETES**

Diabetic patients who had better than LP vision at the baseline assessment tended to benefit from vitrectomy, whereas nondiabetic patients did not (Table 6). In statistical terms, there was a borderline interaction between vitrectomy and diabetes (P = .09) after controlling for other factors related to outcome,7 including baseline visual acuity and vitrectomy.

Nondiabetic patients with better than LP vision at baseline had no advantage to initial vitrectomy: 62.4% achieved 20/40 visual acuity with vitrectomy and 68.7% with tap/biopsy (Table 6). For nondiabetic patients with initial LP-only vision, 32.6% who underwent vitrectomy achieved 20/40 final vision compared with 13.2% who underwent tap/biopsy. Results were similar for other visual thresholds. Thus, just as for the group of all EVS patients,7 in nondiabetic patients there is a clear benefit for vitrectomy for those with LP-only vision.

However, among diabetic patients there is a different trend. For diabetic patients with initial LP-only vision, one third achieved 20/40 final results with vitrectomy compared with none who underwent tap/biopsy. For diabetic patients with better than LP vision at baseline, 57% (12/21) who underwent initial vitrectomy achieved 20/40 final vision compared with 40% (6/15) who underwent tap/biopsy (Table 6). Similar trends are seen for other visual thresholds. These differences were not statistically significant. The number of diabetic patients with better than LP vision at the baseline assessment (and for whom there were final visual results) was small (n = 36).

A treatment interaction was found between IV antibiotic use and diabetes after controlling for all other factors that were identified in the article reporting the main EVS outcomes,7 including the interaction between initial vision and vitrectomy. Data show that IV antibiotics provide no advantage in the nondiabetic group, but in the diabetic group, IV antibiotics are associated with a significantly worse outcome. For example, 13 (52%) of the 25 diabetic patients who did not receive systemic antibiotics and for whom final visual results were available achieved 20/40 vision compared with 8 (36%) of 22 patients who received IV antibiotics.

**COMMENT**

**POPULATION**

Fourteen percent of the 420 EVS patients had diabetes. Phillips and Tasman9 reported the incidence of diabetes was 21% in their series of postoperative endophthalmitis. The definition of diabetes for the EVS was based on whether the patient was taking medicine for glycemic control. The comparison group consisted of 362 patients in the EVS who were not taking diabetic medicines. We recognize that the “nondiabetic” group might well include patients who were diabetic but who did not need systemic medication for diabetic control.

The EVS entry criteria excluded patients if visual acuity before developing cataract was 20/100 or worse. These exclusion criteria may well have eliminated from study entry (and therefore from the population being described in this article) patients with severe diabetic reti-
nopathy. Data from a small previously published retrospective group suggest that diabetic patients with diabetic retinopathy do more poorly after endophthalmitis than those without preexisting retinopathy.3

SYMPTOMS AND SIGNS

The baseline characteristics of diabetic patients were not substantially different from nondiabetic patients except that those with diabetes tended to have slightly worse vision, although the difference was not statistically significant. For example, 74% of diabetic patients had LP or hand motions vision at the initial assessment compared with 70% of nondiabetic patients. Regarding media opacification, a retinal vessel could not be seen in 90% of the diabetic group vs 77% of the nondiabetic group, although this difference was of only borderline statistical significance.

Symptoms and signs were similar in diabetic and nondiabetic patients. Given that neuropathy is a complication of diabetes, one might have expected a lower incidence of pain in the diabetic population, but we did not find that to be the case. Phillips and Tasman6 also found a similar rate of pain in diabetic and nondiabetic patients. For the EVS, the incidence of pain in diabetic patients was 77.6%, and in the article by Phillips and Tasman was 85%. Previous literature reported a slightly greater frequency of hypopyon in diabetic compared with nondiabetic patients. In the EVS, the frequency of hypopyon was approximately equal in diabetic and nondiabetic patients, except that when a hypopyon was present the median height was 50% higher in diabetics.

MICROBIOLOGY

Diabetic patients showed confirmed growth at culture more often than nondiabetic patients (84.5% vs 66.8%). Phillips and Tasman6 reported a similar finding, ie, a greater frequency of positive cultures from diabetic than nondiabetic patients with endophthalmitis, and their data showed a culture-positive rate of 79% in diabetic vs 68% in nondiabetic patients. Similar findings were reported by Bartz-Schmidt et al.10 The fact that culture-positive rate is higher in diabetic patients probably reflects a more permissive environment for bacterial growth in the diabetic eye, with consequent higher bacterial density and perhaps greater number of viable organisms in the diabetic culture sample than from the nondiabetic eye.

Diabetic patients showed a slight tendency to be infected with more virulent organisms, although this was true only for “other Gram-positive” organisms such as Streptococcus and Staphylococcus aureus. Together, Gram-negative and “other Gram-positive” organisms accounted for 26% of diabetic cultures vs 22% of nondiabetic cultures. While Phillips and Tasman6 reported a higher incidence of Gram-negative infection in diabetic patients, the EVS did not find a difference in the prevalence of Gram-negative infection.

The largest difference between diabetic and nondiabetic culture results occurred in the Gram-positive, coagulase-negative group. These were present in 58.6% of diabetics vs 45.0% of nondiabetic cultures. Phillips and Tasman6 also observed a greater prevalence of coagulase-negative organisms in diabetic patients of 50% compared with just over 40% in nondiabetic patients. It is possible the greater frequency of coagulase-negative growth in the diabetic eye may be because these organisms can grow more readily in the diabetic but not in the nondiabetic patient, and therefore in the latter show up as no growth or equivocal growth. The sum of no and equivocal growth cultures and of coagulase-negative cultures was approximately equal for diabetic and nondiabetic patients (74.1% vs 78.2%).

COMPLICATIONS

There was no difference in immediate operative complications among diabetic and nondiabetic patients, and there was no difference in long-term complications such as retinal detachment.

However, diabetic patients required additional surgical procedures after the initial study treatment more often than did the nondiabetic group. This difference mainly occurred in the first week after study entry, when 20.7% of diabetic vs 8.8% of nondiabetic patients required an additional procedure. Since the reasons for early additional procedures generally involved performing a procedure for worsening clinical course, it can reasonably be concluded that diabetic patients were more likely to have a poor initial response to treatment than nondiabetic patients.

VISUAL OUTCOME

At every visual outcome threshold examined, and also along the entire range of visual function, diabetic patients did not have as good a final visual result as nondiabetics (Figure). Phillips and Tasman6 also reported worse visual outcomes in diabetic patients. In their study, 30% of diabetic patients with endophthalmitis became no light perception compared with 8% of the nondiabetic population. In the present study, the numbers were 8% vs 4%, respectively. Phillips and Tasman6 found that 26% of diabetic compared with 59% of nondiabetic patients achieved 20/200 or better vision. Our data show a similar trend of diabetics not doing as well as nondiabetics, but not to the same extent, with 56% of diabetic vs 77% of nondiabetic patients achieving 20/100 or better final vision. In this study, 55% of nondiabetic patients achieved 20/40 vision compared with 39% of diabetic patients. Thus, nondiabetics achieve 20/40 vision 41% more frequently than diabetics. However, the results for diabetic patients are still encouraging since such a high percentage of them do achieve reasonably good results of 20/100 and 20/40. The prognosis for diabetic patients with endophthalmitis is still reasonable, albeit not as good as that for those without diabetes.

Dev et al9 suggest that diabetic patients who develop endophthalmitis but who did not have diabetic retinopathy before developing endophthalmitis have similar visual results to the entire EVS population.7 However, in their study, diabetic patients who had retinopathy before endophthalmitis developed had worse visual results. The study by Dev et al9 was retrospective, included only 12 eyes, and
reported a mixture of endogenous and postoperative cases. We cannot add information regarding this issue since we do not know the diabetic retinopathy status of our patients before they developed endophthalmitis. However, excluded from the EVS were patients who had premorbid ocular conditions other than cataract, which made vision 20/100 or worse. Presumably, these exclusion criteria would have excluded many patients with severe diabetic retinopathy from the EVS. Perhaps if patients with severe retinopathy were also included in the EVS, the results for diabetic patients would have been even worse than we report.

TREATMENT INTERACTIONS

The EVS shows that patients who were diabetic and were treated with IV antibiotics had worse outcomes than diabetics who did not receive IV antibiotics. We cannot explain this result. Possibly it represents a chance variation. However, there is little clinical significance to this finding since systemic antibiotics were not found to be of benefit for treatment of acute postoperative endophthalmitis in the EVS.

For patients with initial LP-only vision, vitrectomy was better than tap/biopsy for patients regardless of whether they were diabetic. For diabetic patients, 33% with initial LP-only vision achieved 20/40 with vitrectomy compared with 0% who underwent tap/biopsy. For nondiabetic patients with initial LP-only vision 33% (15/46) who underwent vitrectomy compared with 13% (5/38) who underwent tap/biopsy achieved 20/40 acuity. Thus, initial vitrectomy was better than tap/biopsy for all patients with LP-only vision at baseline.

Of special interest are the patients who had better than LP vision at the initial assessment. For nondiabetic patients, there was little difference between the final outcomes with initial vitrectomy vs tap/biopsy. Generally one would perform the least invasive procedure, which would be tap/biopsy for nondiabetic patients.

What about diabetic patients who have better than LP vision at baseline? Among such EVS patients, final visual outcome was 20/40 or better for 57% who received vitrectomy compared with only 40% of those who received tap/biopsy. This advantage of vitrectomy over tap/biopsy is seen over the entire range of vision. The finding is supported by results among diabetic patients with initial LP-only vision for whom vitrectomy is markedly superior. The difference in outcome for vitrectomy vs tap/biopsy for diabetic patients with better than LP baseline vision, while clinically important, is not close to being statistically significant in this study. The number of patients with diabetes and better than LP baseline vision for whom final acuity data are available in the EVS is only 36, representing less than 1% power to detect a true difference of 40% vs 57% as statistically significant. Stated differently, there is an 83% chance that with the small sample size we cannot find a statistically significant difference when in fact one exists. To obtain a 90% power (2-sided α .05) to detect such a difference, 360 diabetic patients with better than LP vision would be required, with half assigned at random to vitrectomy and half to tap/biopsy. This would be a 10-fold greater number than the number of patients discussed in this report.

The EVS has the data to raise this clinical question of treatment of endophthalmitis for diabetic patients who have better than LP vision, but does not have sufficient data to answer the question. In our aging society, as the prevalence of diabetes grows, the clinical importance of this question is clear. A clinical trial to test vitrectomy for management of diabetic patients with better than LP vision would be required to definitively answer this question.

Until such a trial is performed, and in the absence of additional data at this time, how should diabetic patients with better than LP baseline vision be treated? Based on the limited data in this report, it would be reasonable to consider vitrectomy as initial treatment for diabetic patients with better than LP vision. However, in the absence of further data, it is also reasonable to treat such patients with tap/biopsy. For nondiabetic patients with better than LP baseline vision, initial vitrectomy provided no additional benefit. As previous EVS data and the data herein support, initial vitrectomy for nondiabetic and diabetic patients alike should be performed on those with LP-only vision.

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