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Long-term effects of cataract surgery with topical levofloxacin on ocular bacterial flora

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Purpose: To clarify the long-term effect of topical antibiotics on the ocular bacterial flora after cataract surgery.

Setting: Miyata Eye Hospital, Miyazaki, Japan.

Design: Prospective case series.

Methods: Patients who had cataract surgery between November 2014 and January 2015 were included. Levofloxacin 1.5% was administered 4 times a day by topical instillation from 3 days before surgery to 1 month postoperatively. The conjunctival sacs of patients were scraped before the procedure and 0, 3, 6, 9, and 12 months after the last instillation. The samples were cultured, and minimum inhibitory concentrations (MICs) of levofloxacin for *Staphylococcus epidermidis* and *Propionibacterium acnes* were evaluated using mixed-effects models.

Results: The study evaluated 50 patients. Diverse bacterial species, predominantly *S epidermidis* and *P acnes*, were isolated before the application of topical levofloxacin. Bacterial diversity was substantially reduced after the final topical levofloxacin application and subsequently increased after 3 months. However, the geometric mean levofloxacin MICs for *S epidermidis* isolates were still significantly higher at 0 months and 3 months than before treatment ($P < .01$ and $P = .03$, respectively) and reached pretreatment levels 6 months and 12 months after the last application. *Propionibacterium acnes* did not show significant changes in the geometric mean levofloxacin MIC over time.

Conclusion: The restoration of the bacterial flora required more than 6 months after cataract surgery and topical levofloxacin.

J Cataract Refract Surg 2017; 43:1129–1134 © 2017 ASCRS and ESCRS

The ocular surface of healthy individuals contains various bacteria such as *Staphylococcus epidermidis* and other coagulase-negative *Staphylococcus*, *Propionibacterium acnes*, and *Corynebacterium*.[1] *Staphylococcus epidermidis* and other coagulase-negative *Staphylococcus* species are important causal pathogens for postoperative endophthalmitis.[2–4] Based on molecular analyses, Speaker et al.[5] and Bannerman et al.[6] showed that these pathogens are derived from the ocular surface flora. To prevent postoperative endophthalmitis, the ocular surface is disinfected by the perioperative administration of topical antibiotics in addition to the direct application of iodine solution during surgery.[7,8] In Japan, many patients having cataract surgery receive topical antibiotic instillations 3 days before to 1 month after surgery.[9] However, the resilience of the ocular surface flora after these clinical interventions for ophthalmologic surgery has not been well investigated.

We recently reported that the duration of perioperative topical levofloxacin administration influences levofloxacin susceptibility of *S epidermidis* isolates from the ocular surface after cataract surgery.[10] Bacterial resistance to antibiotics has become an important clinical and public health issue. The presence of oxacillin-resistant *S aureus* in the conjunctival sac is significantly associated with recent antibiotic use.[11] Three-week administration of topical fluoroquinolones increases the rate of fluoroquinolone-resistant *S epidermidis* isolation from ocular surfaces.[12] However, the fate of these antibiotic-resistant staphylococci after the last topical instillation of antibiotics is unclear.

Submitted: February 23, 2017 | Final revision submitted: June 9, 2017 | Accepted: June 15, 2017

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Supported by Santen Pharmaceutical Co., Ltd., Osaka, Japan.

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0886-3350/$ - see frontmatter
http://dx.doi.org/10.1016/j.jcrs.2017.06.037

The purpose of this paper is to clarify the long-term effect of topical antibiotics on the ocular bacterial flora after cataract surgery.

PATIENTS AND METHODS

This prospective case series study included patients who had cataract surgery in 2014 or 2015. Patients were excluded if they had a history of antibacterial or immunosuppressive medications or ophthalmic surgery within 3 months, ophthalmologic infection, systemic underlying disease, and hospitalization for any reason other than ophthalmic surgery. The study was approved by the Institutional Review Board, Miyata Eye Hospital, Miyazaki, Japan, and was performed in accordance with the tenets of the Declaration of Helsinki and ethical guidelines for clinical research. All patients provided written informed consent after discussion.

Surgical Protocol and Medication Administration

Before surgery, the ocular surfaces were disinfected using 1 minute of irrigation with polyvinyl alcohol–iodide solution and washed with sterile 0.9% sodium chloride. Topical instillation of levofloxacin 1.5% (Cravit) 4 times per day was initiated on the third preoperative day.[13] On the day of surgery, eyedrops were administered in the morning and 1 hour before surgery. For 1 month after surgery, levofloxacin 1.5% was administered 4 times a day. Oral cefcapene pivoxil 300 mg/day (Flomox) was administered to the patients for 3 days after surgery.

Bacteriologic Analysis

A bacteriologic examination was performed on samples scraped from the conjunctival sac under surface anesthesia with preservative-free oxybuprocaine hydrochloride before the start of topical levofloxacin administration and 0 month (after the last levofloxacin treatment), 3 months, 6 months, 9 months, and 12 months after the postoperative instillation of antibiotics. This timing was equivalent to 1 month, 4 months, 7 months, 10 months, and 13 months after surgery, respectively.

Specimens were examined by direct culture and liquid culture under aerobic and anaerobic conditions. The aerobic culture was performed at 36.5°C for 24 to 48 hours in trypticase soy agar with Columbia colistin, nalidixic acid agar, and 5% sheep blood (Becton Dickinson Co.), Columbia agar with 5% sheep blood (Becton Dickinson Co.), and chocolate agar (Kyokuto Pharmaceutical Industrial Co. Ltd.). The anaerobic culture was performed at 36.5°C for 24 to 120 hours using Columbia agar with 5% sheep blood under anaerobic conditions. The liquid culture was performed in thioglycolate broth at 36.5°C for 1 to 2 weeks.

Each bacterial isolate was evaluated to determine the minimum inhibitory concentrations (MICs) of levofloxacin in accordance with the broth microdilution method described in the Clinical and Laboratory Standards Institute Standards.[14] The MICs of levofloxacin were determined using antibiotic susceptibility tests with the SG17 plate (Eiken Chemical).[15] For *Staphylococcus* species; the MIC of oxacillin was measured to identify isolates as methicillin-susceptible or methicillin-resistant.

Statistical Analysis

Data obtained from the pretreatment visit to the final 12-month visit were used for the analysis. To estimate the differences between the number of bacterial species before surgery and the counts at other timepoints, mixed-effects models were used with the number of bacterial species as a response variable, visit as a fixed effect, and patient as a random effect. To estimate the geometric mean MICs of levofloxacin on *S epidermidis* and *P acnes* at each visit and the mean changes from preoperatively, mixed-effects models were used with log-transformed MICs as a response variable, visit as a fixed effect, and patient as a random effect. The estimated geometric mean MICs are reported with 95% confidence intervals. The influence of background factors on isolates was evaluated using a generalized estimating equation (GEE) logistic model. Statistical analyses were implemented in SAS software (version 9.4, SAS Institute, Inc.). A P value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

This study enrolled 50 patients. The mean age of the 29 women and 21 men was 74.4 years $\pm$ 7.4 (SD) (range 56 to 88 years). The initial operated eye was examined bacteriologically in patients who subsequently received contralateral surgery within the study period. All 50 patients were followed for at least 6 months after the last topical levofloxacin treatment. One patient could not be followed after 9 months, and 2 patients could not be followed after 12 months. No patient developed blepharitis or postsurgical infection.

Bacterial Isolates

Before topical levofloxacin was administered, bacteria were isolated from 48 of 50 eyes by direct and/or liquid culture methods (Table 1). Single or multiple strains were isolated from many eyes at 3, 6, 9, and 12 months after the last levofloxacin treatment, but either no strains or single strains were isolated immediately after the last levofloxacin treatment (0 month). In a mixed-effects model, the percentage of eyes that were positive for bacterial isolates was significantly lower at 0 month (after the last levofloxacin treatment) than before antibiotic administration ($P < .01$) (Figure 1). However, no significant changes were observed 3, 6, 9, or 12 months after the last levofloxacin treatment.

Isolated Bacterial Species

Various species were frequently isolated from the conjunctival sac before the start of topical levofloxacin treatment (Tables 1 and 2). *Staphylococcus epidermidis* (33.3%) and *P acnes* (33.3%) were the predominant species detected. Immediately after the last levofloxacin treatment (0 month), the bacterial diversity of the conjunctival sac was substantially reduced and *P acnes* became the predominant isolate. Three months after the last levofloxacin treatment, bacterial diversity in the conjunctival sac was similar to that observed before the first levofloxacin treatment (Figure 2). In a GEE logistic model, a significant decrease in diversity was observed at 0 month only.

Antibiotic Susceptibility of Isolates

Regarding changes in the levofloxacin MIC of *S epidermidis*, the mean geometric MIC was significantly higher at 0 month than before the initial levofloxacin treatment (Figure 3). Thereafter, the mean MIC values decreased and did not differ significantly from the initial value. The levofloxacin MIC of *P acnes* showed no significant differences before and after topical levofloxacin administration (Figure 3).

In an analysis of the cumulative percentage of levofloxacin MICs for all *S epidermidis* isolates at each timepoint, single-step increases were consistently observed at approximately 4 μg/mL (Figure 4). The cumulative percentage was lower for isolates 3 months and 6 months after the last levofloxacin than for other isolates below 4 μg/mL.