Subconjunctival Delivery of Antibiotics in a Controlled-Release System

A Novel Anti-infective Prophylaxis Approach for Cataract Surgery

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Objective: To compare the efficacy of subconjunctival injection of a combination of triamcinolone and ciprofloxacin hydrochloride, 2 mg/0.1 mL, in a controlled-release system (DuoCat) with that of ciprofloxacin hydrochloride, 0.3%, eyedrops for infection prophylaxis.

Methods: Rabbit eyes were injected subconjunctivally with a combination of triamcinolone and ciprofloxacin hydrochloride, 2 mg/0.1 mL, or ciprofloxacin hydrochloride, 2 mg/0.1 mL, alone. The aqueous and vitreous humor pharmacokinetic profiles were compared with those of a single drop of ciprofloxacin hydrochloride, 0.3%, 6 times daily. In 45 rabbits, *Staphylococcus aureus* was injected into the anterior chamber: 15 randomly received 1 drop of ciprofloxacin hydrochloride, 0.3%, every 4 hours during 24 hours; 15 received drops of balanced salt solution; and 15 received a combination of triamcinolone and ciprofloxacin hydrochloride, 2 mg/0.1 mL. After 24 hours, endophthalmitis scores were recorded, aqueous and vitreous humors underwent culture, and histologic analysis was performed.

Results: The combined triamcinolone and ciprofloxacin treatment allowed higher intraocular levels of ciprofloxacin. The median endophthalmitis clinical scores for the combination of triamcinolone and ciprofloxacin and ciprofloxacin-only eyedrop groups were equivalent ($P = .42$) and were significantly lower than those of the balanced salt solution group ($P < .001$). The culture was negative for *S aureus* in the combined triamcinolone and ciprofloxacin and ciprofloxacin eyedrop regimens. No adverse effects were observed with either route.

Conclusions: Ciprofloxacin eyedrops and combined triamcinolone and ciprofloxacin were equally tolerated and efficacious. The combined triamcinolone and ciprofloxacin treatment may eliminate noncompliance issues and may prove to be a valuable clinical tool for surgical prophylaxis.

Clinical Relevance: The combined triamcinolone and ciprofloxacin treatment may be a new useful strategy for surgical prophylaxis.

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THE USE OF TOPICAL ANTIBIOTIC drugs poses unique and challenging hurdles for drug delivery,[1-3] and, beyond antibiotic potency, alternative means of enhancing protection against infection during cataract surgery should be explored. A potential barrier to topical delivery is diffusion through the cornea.[2,3] Exploiting the permeability of the sclera, subconjunctival routes may offer a promising alternative to boost drug penetration and tissue targeting.[4-9] In theory, the combination of an antibiotic agent with an anti-inflammatory drug in a controlled-release system delivered transsclerally could be used after cataract surgery to eliminate postoperative topical medication use, enhancing patient compliance and improving drug penetration and bioavailability.

In this experimental study, we tested the feasibility of a biodegradable transscleral drug delivery system as a more comprehensive anti-infective prophylaxis approach for cataract surgery. We compared the drug tolerance and intraocular bioavailability of one subconjunctival injection of ciprofloxacin hydrochloride, 2 mg, loaded in a controlled-release microsphere system with triamcinolone with those of one subconjunctival injection of combined ciprofloxacin, 2 mg, in its free form and ciprofloxacin hydrochloride, 0.3%, eyedrops using a dosing regimen that simulated prophylactic use after cataract surgery. The study also investigated the potential of these ciprofloxacin delivery approaches to prevent bacterial endophthalmitis when the anterior chamber was challenged with *Staphylococcus aureus*.

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METHODS

Overall, 223 female New Zealand white rabbits of similar age and weight (2.0-2.5 kg) were used. A total of 160 animals were used for the drug bioavailability study: 32 were assigned to the eyedrop group (4 animals were humanely killed hourly for 8 hours), 64 were assigned to the regular ciprofloxacin subconjunctival injection group (4 animals were humanely killed hourly for the first 12 hours and 4 animals 24, 36, 48, 72, 120, 168, and 240 hours after injection), and 64 were assigned to the combined triamcinolone and ciprofloxacin (DuoCat) group (4 animals were humanely killed hourly for the first 12 hours and 4 animals 24, 36, 48, 72, 120, 168, and 240 hours after injection). Preliminary studies were required to determine the amount of *S aureus* necessary to reproducibly create a clinical picture consistent with endophthalmitis (12 animals). The prophylactic experiment (57 rabbits) was then designed to test 2 different ciprofloxacin prophylactic approaches (ciprofloxacin eyedrops [15 rabbits] and combined triamcinolone and ciprofloxacin treatment [15 rabbits]) compared with the control group (balanced salt solution [BSS] drops [15 rabbits]). For the histologic analysis, 6 additional rabbits were used. All the animals were treated in compliance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research, and a detailed elucidation of the methods used in the entire investigation appears in the following subsections.

CIPROFLOXACIN MICROSPHERES

Preparation and Characterization

Triamcinolone was purchased from Sigma-Aldrich, Inc, St Louis, Missouri; ciprofloxacin hydrochloride was purchased from Galena (Campinas, Brazil); and polylactic-co-glycolic acid (PLGA) 50:50 (inherent viscosity, 0.63 dL/g at 30°C) from Birmingham Polymer Inc (Birmingham, Alabama). Acetone and glacial acetic acid were obtained from Merck SA (Rio de Janeiro, Brazil). Water was prepared using a water purification system (Milli-Q Plus; Millipore Corp, Billerica, Massachusetts), and its resistivity was 18.2 MΩ·cm.

The ciprofloxacin microspheres were prepared using a spray-drying method in a mini spray dryer (Büchi-191 Laboratory Apparatus; BÜCHI Labortechnik AG, Flawil, Switzerland). Ciprofloxacin was dissolved in glacial acetic acid and was added to acetone solutions of polymer to obtain an adequate proportion of drug to polymer for the microspheres. The ciprofloxacin-loaded PLGA microspheres were analyzed using scanning electron microscopy. The mean size was determined using photomicrography in Leica QWin software (Leica Microsystems GmbH, Wetzlar, Germany).

Drug Encapsulation Efficiency

Ciprofloxacin-loaded PLGA microspheres with ciprofloxacin content of 2 mg were dissolved in 10 mL of glacial acetic acid and diluted in 0.1M acetic acid to obtain a ciprofloxacin concentration of 10 µg/mL. The amount of the encapsulated drug was determined by means of high-performance liquid chromatography (HPLC) using a Waters Alliance 2695 chromatograph (Waters Corp, Milford, Massachusetts). The drug encapsulation efficiency was calculated from the ratio between the analytical and theoretical drug contents in the microspheres.

Sterilization

The ciprofloxacin-PLGA microspheres were sterilized by means of γ-irradiation. The spheres were kept in 3-mL multidose polypropylene tubes and irradiated in air at a rate of 230 Gy/min using a Picker V 90 60Co source (Picker International Inc, Cleveland, Ohio) (to convert to rads, multiply by 100), for a total dose of 25 kGy.

BIOAVAILABILITY STUDY

Treatment Groups and Assessment

One hundred sixty New Zealand albino rabbits were used. Anesthesia consisted of an intramuscular injection of combined ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg) during all procedures, with additional ketamine injections as needed. One eye of each animal was randomly allocated to receive either a single ciprofloxacin hydrochloride, 0.3%, eyedrop every 4 hours (32 eyes) or 2 mg of regular ciprofloxacin hydrochloride as an inferior subconjunctival injection (64 eyes) or 2 mg of ciprofloxacin-PLGA microspheres as an inferior subconjunctival injection (64 eyes). Measurements were performed hourly during the first 8 hours for all groups and at 12, 24, 36, 48, 72, 120, 168, and 240 hours thereafter for the groups that received the subconjunctival injection. The eyes were then enucleated using deep anesthesia, frozen immediately, and stored at –80°C. The animals were humanely killed using an intravenous injection of pentobarbital sodium (50 mg/kg).

Ciprofloxacin HPLC Assay

Quantitative analysis was performed using HPLC (Waters Alliance 2695 chromatograph; Waters Corp), with a UV-visible detector at 278 nm and a C18 column width of 150 × 4.0 mm, a particle size of 5 µm, and a pore size of 18 nm. The mobile phase was an acetonitrile-phosphoric acid solution (2.45 g/L, pH=3.0 adjusted with triethanolamine), 13/87 vol/vol. The concentration of the released ciprofloxacin was determined in the aqueous and vitreous humors up to 10 days. For quantitative analysis, the samples were centrifuged at 15 000*g*, and 50 µL of the supernatant solution was injected into the HPLC system using an automatic injector.

PROPHYLAXIS STUDY

The right eye of 57 female New Zealand white rabbits (2.0-2.5 kg) was used. Twelve rabbits divided into 4 groups of 3 rabbits each were used to determine the number of staphylococcal colony-forming units (CFUs) that would be used in the remaining 45 rabbits.

S aureus Isolate

A clinical isolate of *S aureus* was recovered from the vitreous culture of a patient diagnosed as having endophthalmitis. β-Hemolytic activity on trypticase soy agar containing 10% sheep blood and its gram-positive, catalase-positive, coagulase-positive profile identified this isolate as *S aureus*. Susceptibility testing demonstrated that the isolate was susceptible to ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin hydrochloride, erythromycin, clindamycin, and vancomycin hydrochloride. The minimum inhibitory concentration of the bacterial isolate to ciprofloxacin was 0.51 µg/mL.

Preparation of *S aureus* Inoculum

An overnight suspension of *S aureus* was made in saline equivalent to a McFarland 1 turbidity standard (Remel, Lenexa, Kansas), representing approximately 2×10^8 CFU/mL, and the sus-

pension was diluted in ratios of 1:10, 1:100, and 1:1000 in trypticase soy broth to final concentrations of 2×10^7, 2×10^6, and 2×10^5 CFU/mL, respectively. These inocula were packed on ice and were immediately injected into the anterior chamber of 3 rabbits per inoculum (5×10^7, 5×10^6, 5×10^5, and 5×10^4 CFU per rabbit eye) using a 30-gauge needle attached to a 0.5-mL syringe and delivering an inoculum volume of 0.025 mL. This preliminary study revealed that a 2×10^8-CFU/mL dilution (5×10^7 CFU per eye) was necessary to reproducibly create a clinical picture consistent with endophthalmitis under these conditions and, thus, became the inoculum for the study of the remaining 45 rabbits.

Inoculum Injection

The anterior chamber bacterial challenge was used as a simulation of intraocular infection during surgery. The challenge dose of *S aureus* of 2×10^8-CFU/mL dilution (5×10^7 CFU in 0.025 mL per eye) was injected into the anterior chamber of 45 rabbits. After the injection, the rabbits were randomly assigned to 1 of 3 treatment groups: 15 rabbits received 1 drop of BSS immediately after injection and at 4, 8, 12, 16, 20, and 24 hours; 15 rabbits received 1 drop of ciprofloxacin hydrochloride, 0.3% (Ciloxan; Alcon Laboratories, São Paulo, Brazil), following a similar regimen; and 15 rabbits received a subconjunctival injection of ciprofloxacin hydrochloride, 2 mg, loaded in a controlled-release microsphere system.

Endophthalmitis Evaluation

Twenty-four hours after the anterior chamber infection, the eyes were examined and graded in a masked manner in accord with the criteria described by Kowalski et al.[10] Clinical signs of endophthalmitis (iritis, hypopyon, conjunctivitis, ciliary injection, blepharitis, anterior chamber cells, anterior chamber flare, corneal infiltrate, red reflex, and fibrin) were evaluated and scored using a scale based on increasing severity (0, 1, 2, and 3), and a composite score was created based on the sum of these clinical sign scores. At the end of the examination, all the rabbits were anesthetized, and, using sterile conditions, the aqueous and vitreous materials were aspirated using a 27-gauge needle on a tuberculin syringe to determine the number of viable bacteria using standard colony count dilution methods.

Safety of Periocular Microspheres

Safety was assessed by visual inspection and by histologic analysis between normal rabbits injected with BSS and normal rabbits injected with ciprofloxacin microspheres. For the histologic analysis, 6 rabbits were used. Fifteen and 30 days after the subconjunctival injection, the rabbits were deeply anesthetized as described in the "Treatment Groups and Assessment" subsection. The eyes were enucleated, and the conjunctiva and periocular tissues were removed and immersed in a 10% formalin solution for 24 hours. After rehydration, the tissues were stained with hematoxylin-eosin or Masson trichrome and were viewed through a microscope (Axioscope 40; Carl Zeiss Meditec Inc, Dublin, California).

STATISTICAL ANALYSIS

For the bioavailability study, comparisons of drug levels were performed using analysis of variance followed by the *t* test. For the prophylaxis study, the Kruskal-Wallis test was used to compare the scores among the groups. In cases in which the result of this test was statistically significant ($P<.05$), the groups were compared in pairs using the Mann-Whitney test. Exact *P* values adjusted for ties were used in the analyses. The Fisher exact test was used to compare the results of the bacteria culture between groups. For the bioavailability and prophylaxis studies, the type I error was set at $\alpha=.05$.

RESULTS

The spray-drying solvent evaporation technique produced ciprofloxacin-PLGA microspheres that were uniform in size and shape. The mean (SD) particle size was 1.03 (0.30) µm, and the mean (SD) encapsulation efficiency was 97.86% (0.96%).

BIOAVAILABILITY STUDY

Compared with the ciprofloxacin solution and ciprofloxacin eyedrop groups, drug levels in the microsphere group showed an immediate and sustained trend toward increased aqueous and vitreous penetration (**Figure 1**). Comparing the aqueous concentration after a single subconjunctival injection of the ciprofloxacin-loaded microspheres with that of the regular ciprofloxacin formulation, a significant difference in favor of the microsphere group was immediately noticed after drug administration and was sustained throughout the entire study ($P<.04$). The combined triamcinolone and ciprofloxacin treatment allowed a sustained aqueous humor concentration of ciprofloxacin in the therapeutic range for most common ocular pathogens (2 µg/mL) for up to 8 days. A parallel pharmacokinetic trend was observed when the microsphere group was compared with the topical administration group. In the 8 hours studied for this group, an immediate higher intraocular antibiotic level favoring the microsphere group was observed ($P<.04$), except at the fifth hour, which demonstrated comparable measurements ($P=.04$) (Figure 1A). At this time point, 1 hour before sampling, an extra drop of ciprofloxacin was instilled, following the preestablished schedule of 1 loading drop every 4 hours.

In contrast to the combined triamcinolone and ciprofloxacin and eyedrop groups, no measurable levels of ciprofloxacin could be detected in the vitreous cavity after topical administration. Assessing the vitreous concentration, a significant difference in favor of the microsphere group was immediately noticed after drug administration and was sustained throughout the entire study (Figure 1B) ($P<.87$).

PROPHYLAXIS STUDY

The **Table** compares the clinical scores in the study groups. The median (range) composite score in the eyedrop group was 18 (12-26), in the microsphere group was 18 (10-24), and in the BSS group was 25 (21-28) ($P<.001$). The BSS group had a significantly higher composite score than did the eyedrop and microsphere groups ($P<.001$ for both). The composite scores of the eyedrop and microsphere groups were not significantly different ($P=.42$). **Figure 2** shows typical clinical photographs of the rabbit eyes in the 2 treatment groups.

The results of the aqueous ($P<.001$) and vitreous ($P=.03$) humor cultures were different among the 3 study

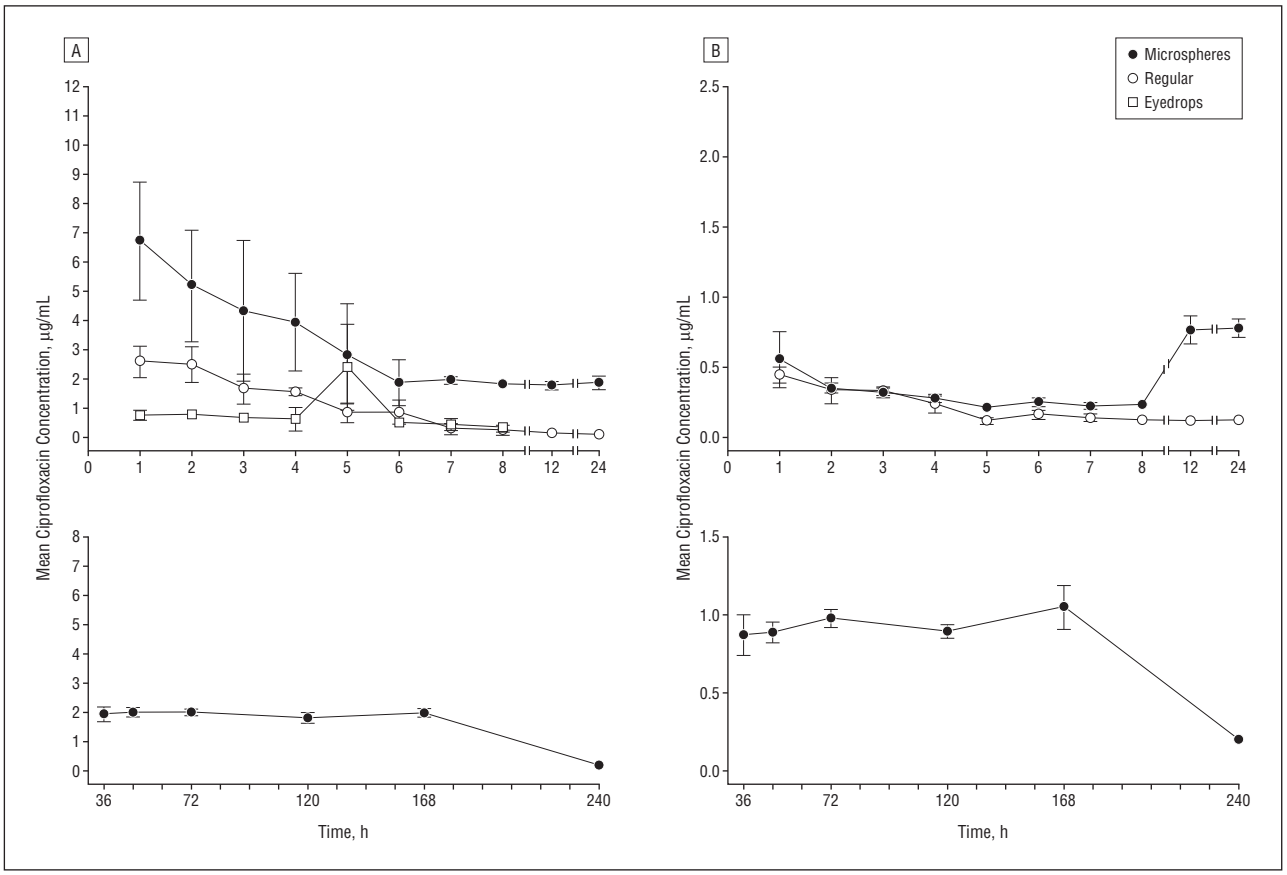

Figure 1. Ciprofloxacin concentration profile in the aqueous (A) and vitreous (B) humors of the microsphere, regular subconjunctival, and eyedrop groups. Error bars represent 1 SD.

groups. Both ciprofloxacin-treated groups (eyedrops and combined triamcinolone and ciprofloxacin) had negative cultures in the aqueous and vitreous humors in all the eyes challenged with bacteria. Although all 15 eyes in the BSS group initially clinically had endophthalmitis, 9 eyes were positive for bacterial growth in the aqueous humor culture and only 4 eyes were positive in the vitreous humor culture.

Inspection of the injection site did not reveal the presence of any inflammation, including redness and edema, for rabbits injected with a combination of triamcinolone and ciprofloxacin. Masson trichrome staining of the periocular tissue including the conjunctiva revealed no difference in the collagen staining patterns between control rabbits and rabbits injected with a combination of triamcinolone and ciprofloxacin.

COMMENT

This study discloses pioneering information and substantiates a novel antibiotic prophylaxis strategy using slow-delivery technology. Superior vitreous penetration and an immediately higher concentration of antibiotic in the aqueous humor compared with the common practice of dosing ciprofloxacin, 0.3%, eyedrops 6 times daily support and add rationale to the use of a slow-release transscleral drug delivery system in preventing endophthalmitis after cataract surgery. In addition, when this pharmacologic achievement is coupled with its ability to free the patient of the nuisance of topical administration, a clear role for combined triamcinolone and ciprofloxacin as a simple and more comprehensive weapon for fighting postoperative infections begins to emerge.

The use of topical antibiotic agents poses fairly challenging hurdles and unique constraints to ocular drug delivery.[1] In the present study, ciprofloxacin, in a regimen that simulates a real-life postoperative dosing schedule, was not detected in the vitreous. Fourth-generation fluoroquinolones possess several important therapeutic attributes, such as high potency and penetration. However, the multiple loading doses considered in most fourth-generation fluoroquinolone studies[11-13] do not address a realistic scenario, and may solely provide a surrogate to assess achievable postoperative concentrations but not to anticipate accuracy. Frequency of application is important for attaining adequate antibacterial concentrations, and poor compliance also prevents the eyedrops from reaching efficacious levels.[14] Targeting the ultimate level of anti-infective protection, beyond antibiotic spectrum and potency, alternative means of optimizing drug delivery, bioavailability, and patient compliance should be investigated.

By exploring superior sclera permeability and to avoid the rate-limiting barriers of the cornea and conjunctiva, subconjunctival routes may offer a promising alternative for enhanced drug delivery and tissue targeting com-

Table. Clinical Scores of the Combined Triamcinolone and Ciprofloxacin Microsphere System; Ciprofloxacin, 0.3%, Eyedrops; and Balanced Salt Solution (BSS) Treatment Regimens 24 Hours After *Staphylococcus aureus* Injection Into the Anterior Chamber

Variable and Score	Group, No. (%)			*P* Value			
	Eyedrops (n=15)	Microspheres (n=15)	BSS (n=15)	Among the 3 Groups	Eyedrops vs Microspheres	Eyedrops vs BSS	Microspheres vs BSS
Eyelid margin injection				<.001	.003	.14	<.001
0	2 (13)	9 (60)	0				
1	8 (53)	6 (40)	6 (40)				
2	5 (33)	0	9 (60)				
3	0	0	0				
Conjunctival erythema				<.001	.74	.004	.001
0	0	0	0				
1	6 (40)	7 (47)	0				
2	7 (47)	7 (47)	7 (47)				
3	2 (13)	1 (7)	8 (53)				
Ciliary injection				.001	.86	.003	.004
0	0	0	0				
1	4 (27)	3 (20)	0				
2	8 (53)	9 (60)	4 (27)				
3	3 (20)	3 (20)	11 (73)				
Corneal infiltrate				<.001	.37	.001	<.001
0	0	0	0				
1	5 (33)	7 (47)	0				
2	8 (53)	8 (53)	4 (27)				
3	2 (13)	0	11 (73)				
Iritis				.09			
0	0	0	0				
1	0	1 (7)	0				
2	8 (53)	3 (20)	2 (13)				
3	7 (47)	11 (73)	13 (87)				
Anterior chamber flare				>.99			
0	0	0	0				
1	0	0	0				
2	0	0	0				
3	15 (100)	15 (100)	15 (100)				
Fibrin				.16			
0	1 (7)	3 (20)	0				
1	4 (27)	3 (20)	0				
2	5 (33)	5 (33)	9 (60)				
3	5 (33)	4 (27)	6 (40)				
Anterior chamber cells				>.99			
0	0	0	0				
1	0	0	0				
2	0	0	0				
3	15 (100)	15 (100)	15 (100)				
Hypopyon				<.001	.47	<.001	<.001
0	12 (80)	14 (93)	0				
1	2 (13)	1 (7)	6 (40)				
2	1 (7)	0	9 (60)				
3	0	0	0				
Red reflex				.006	.53	.04	.002
0	1 (7)	3 (20)	0				
1	5 (33)	3 (20)	0				
2	7 (47)	9 (60)	11 (73)				
3	2 (13)	0	4 (27)				

pared with topical routes.[4-9] Confirming our premise, the combination of triamcinolone and ciprofloxacin delivered therapeutic concentrations greater than the minimum inhibitory concentration for most common ocular pathogens up to 10 days after injection. The combined triamcinolone and ciprofloxacin dosing regimen tested in this experimental investigation fits into a realistic clinical scenario and may provide a surrogate to assess achievable postoperative concentrations. Similar to previous studies,[15-17] the parallel and higher aqueous and vitreous levels of ciprofloxacin-loaded microspheres, as opposed to the same concentration of ciprofloxacin in its free form after a single subconjunctival injection and to topical ciprofloxacin delivery, are considered a highly desirable pharmacologic achievement. A trend favoring combined triamcinolone and ciprofloxacin treatment over eyedrop administration is suggested by these data, and future studies may confirm this initial evidence. Furthermore,

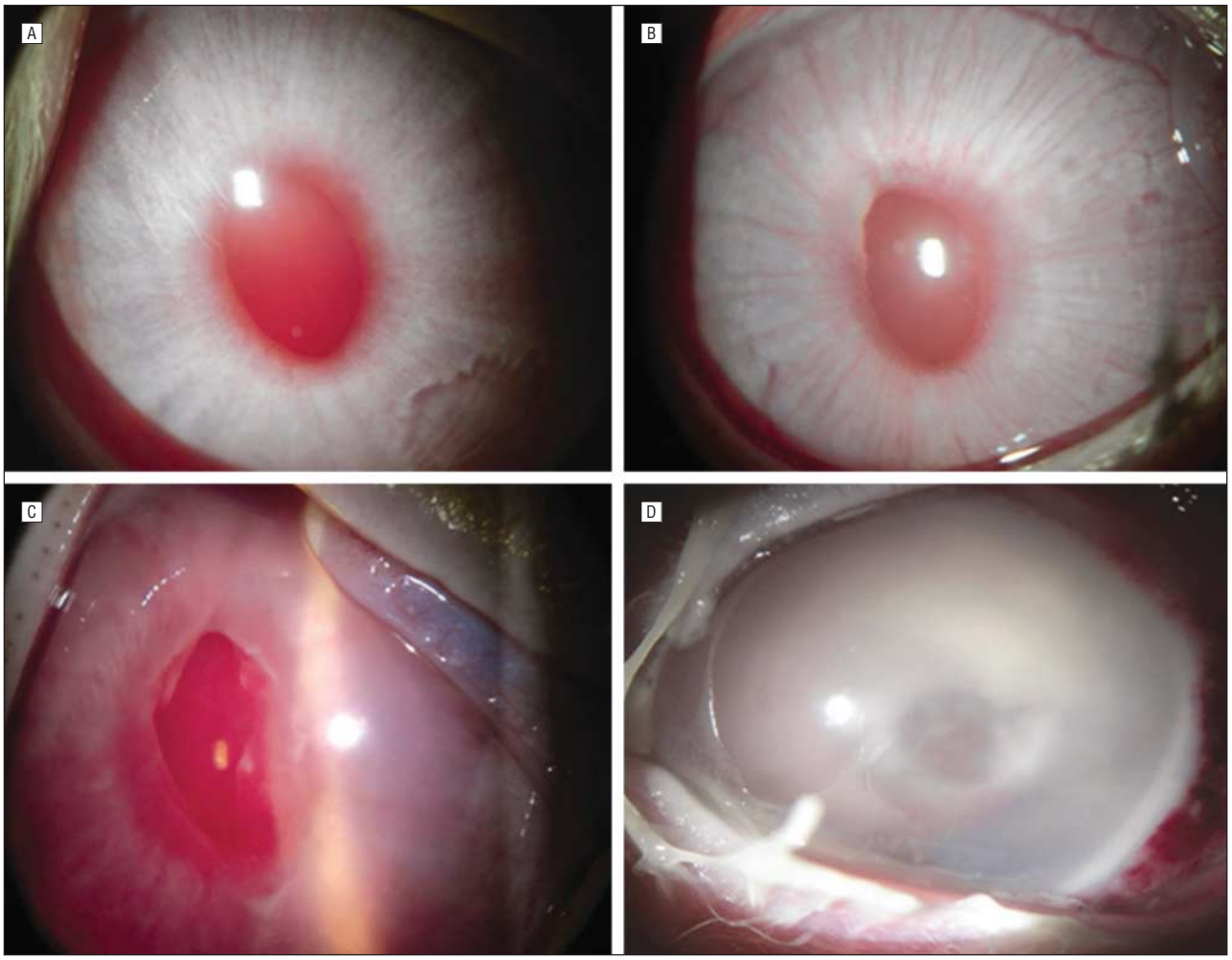

Figure 2. Slitlamp photographs of representative eyes of rabbits taken 24 hours after anterior chamber inoculation with *Staphylococcus aureus* (5×10^7 colony-forming units). A, A single subconjunctival injection of 2-mg/0.1 mL ciprofloxacin-loaded polylactic-co-glycolic acid microspheres (combined triamcinolone and ciprofloxacin) immediately after infection. B, One drop of ciprofloxacin, 0.3% (commercial preparation), immediately after infection and repeated at 4, 6, 10, 14, 16, 20, and 24 hours. C and D, One drop of balanced salt solution (commercial preparation) using the same treatment regimen as in (B). Note the increased reaction around the pupil in the balanced salt solution–treated eyes (C and D) compared with the triamcinolone and ciprofloxacin–treated eyes (A) and the ciprofloxacin, 0.3%, eyedrop–treated eyes (B).

given the inherent advantages of intraoperative sustained-release antibiotics, particularly regarding patient compliance and convenience, combined triamcinolone and ciprofloxacin treatment may achieve a breakthrough in the development of more successful treatment modalities, suggesting a possible new way to progress anti-infective prophylaxis in parallel with antibiotic drug development.

In the prophylaxis study, we demonstrated the "proof of principle" that prophylaxis with combined triamcinolone and ciprofloxacin can reach sustained therapeutic levels in the anterior chamber that predictably reduce bacterial recovery and signs of clinical endophthalmitis (comparable with conventional topical eyedrops) in an animal model. Extrapolating these findings to clinical settings, where patients typically are noncompliant with treatment, we could postulate and expect a potential superior performance of combined triamcinolone and ciprofloxacin over conventional postoperative eyedrops. This is also a cost-effective intervention and potentially opens a large avenue for future and mandatory investigation to validate the initial findings.

A low adverse event rate is an important concern with any new dosage form. The biocompatibility of periocular microspheres of biodegradable polymers has been extensively investigated.[18,19] In the present study, no drug- or procedure-related adverse events occurred, and we did not observe any inflammatory cells or fibrous tissue response at the injection site. In humans, the combined triamcinolone and ciprofloxacin treatment system has shown high degrees of safety and tolerability not affecting the successful healing of the cornea after surgery.[20]

In conclusion, a single dose of subconjunctival ciprofloxacin-PLGA microspheres sustained aqueous and vitreous therapeutic levels for up to 10 days. The study findings neither advocate nor support the use of combined triamcinolone and ciprofloxacin as a prophylaxis agent for cataract surgery but suggest that ciprofloxacin in conventional postoperative eyedrops and combined triamcinolone and ciprofloxacin subconjunctival injection may be equally tolerated and efficacious. In parallel with antibiotic drug development, exploiting the routes of transscleral delivery and circumventing the cornea-con-

junctival barriers will be key to an ultimate anti-infective strategy in the modern era of cataract surgery. Although the challenges are formidable, these data hold promise for new paradigms in dosing anterior segment drugs.

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