

# The Effects of Topical Moxifloxacin 0.5% Ophthalmic Solution and Gatifloxacin 0.3% Solution on Corneal Healing After Bilateral Photorefractive Keratectomy

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**Purpose:** This study was designed to evaluate the effects of topical moxifloxacin 0.5% ophthalmic solution (Vigamox) and gatifloxacin 0.3% ophthalmic solution (Zymar) on corneal wound healing for patients undergoing bilateral photorefractive keratectomy (PRK).

**Methods:** Forty-three patients with low-to-moderate myopia ( $-1.00$  to  $-7.00$  D), ranging from 21 to 71 years of age, were randomized into 2 groups: moxifloxacin ( $n = 21$ ) and gatifloxacin ( $n = 22$ ). After bilateral PRK, antibiotics were administered in both eyes (fellow-eye design) immediately and then every 6 hours until complete wound healing had occurred. Slit-lamp fluorescein pictures were taken of each eye immediately after surgery and on postoperative days until complete wound healing had taken place. NIH software (Image J) was used to measure surface area of the defect.

**Results:** Analysis showed no difference in the time of wound closure ( $P = 0.79$ ). The mean healing rate for moxifloxacin was  $0.8 \text{ mm}^2/\text{h} \pm 0.2$  (mean  $\pm$  standard deviation), and  $0.8 \text{ mm}^2/\text{h} \pm 0.2$  for gatifloxacin. There were no differences in the healing rates ( $P = 0.61$ ), haze ( $P > 0.09$ ), or in the postoperative uncorrected visual acuity ( $P > 0.66$ ) at 1 month.

**Conclusion:** Moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% ophthalmic solution produced similar results with respect to haze, visual acuity, and rate of corneal wound healing when administered to PRK patients.

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Increasing reports of emerging ocular bacterial resistance have prompted the development of the new fourth-generation fluoroquinolone antibiotics, moxifloxacin 0.5% ophthalmic solution (Vigamox, Alcon Laboratories, Inc., Fort Worth, TX) and gatifloxacin 0.3% ophthalmic solution (Zymar, Allergan Inc., Irvine, CA). These therapeutic agents are approved for the treatment of bacterial conjunctivitis.<sup>1,2</sup>

In vitro studies using endophthalmitis isolates by Mather and colleagues<sup>3</sup> have shown that moxifloxacin and gatifloxacin are more potent than earlier-generation fluoroquinolones against gram-positive bacteria while retaining similar potency for gram-negative species. These authors suggested that moxifloxacin and gatifloxacin have utility in the treatment of ocular infections and in the prevention of postsurgical endophthalmitis. Katz<sup>4</sup> reported successful treatment of a *Pseudomonas aeruginosa* contact lens-related corneal ulcer in a human patient.

As these fluoroquinolone antibiotics gain acceptance for treatment and prophylaxis against ocular infections, published studies on their effects on corneal wound healing gain increasing importance to clinicians. Our group has undertaken and recently reported in vitro and in vivo studies using immortalized cultured human corneal epithelial cells, followed by animal models of corneal wound healing, respectively.<sup>5</sup> This report here examines the effects of moxifloxacin and gatifloxacin of corneal wound healing in patients undergoing PRK.

There are few published studies on the effects of moxifloxacin 0.5% and gatifloxacin 0.3% on the corneal wound process in humans. Our studies were undertaken to further confirm the results from our in vitro and in vivo animal model studies. The data from this report provide important evidence on the utility of moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% ophthalmic solution for patients undergoing PRK.

## MATERIALS AND METHODS

Institutional review board approval was obtained before initiation of the study. Patients ranging in age from 18 years with mild-to-moderate myopia ( $-1.00$  to  $-7.00$  diopters) and mild astigmatism (up to 1.50 diopters) were eligible for this study (Table 1 lists exclusive criteria).

The patients were randomized via coin toss into 2 treatment groups (moxifloxacin,  $n = 21$  eyes, and gatifloxacin,  $n = 22$  eyes). Three days before surgery, all patients were administered their assigned antibiotic 4 times per day in a masked fashion.

All patients underwent standardized 9.0-mm chemical debridement PRK by the same surgeon by using 20% alcohol for 60 seconds. No soft contact lenses or patches were used in this protocol. Postoperatively, all patients were administered in

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**TABLE 1. Exclusion Criteria**

Current use of nonsteroidal anti-inflammatory agents, corticosteroids, anticoagulants, or serum products
Sensitivity or poor tolerance to any component of the study treatment
Dry eyes, ie, Schirmer <10 mm and/or any corneal staining with rose bengal
Pregnant, nursing, or attempting to become pregnant
Use of any of the investigational products within the last 30 d
Have worn soft contact lenses within past 7 d or hard contact lenses within 30 d
Systemic antihistamines
Uncontrolled systemic disease

a masked fashion their assigned antibiotic (fellow-eye design) and Pred Forte 1% 4 times per day for 7 days in both eyes. Digital photos of the corneal wounds stained with fluorescein were taken with cobalt blue light immediately after surgery at 9:00 AM on the first day after surgery, and 9:00 AM and 3:00 PM on every day thereafter until the wound completely healed. The images were recorded and analyzed using a computer planimetry program. Wound areas (in square millimeters) were recorded and compared between the 2 treatment groups by an independent reader in a masked fashion. The square root transformations were applied to the wound area to obtain a constant healing rate. Statistical comparisons were analyzed using an analysis of variance test by an independent statistician in a masked fashion.

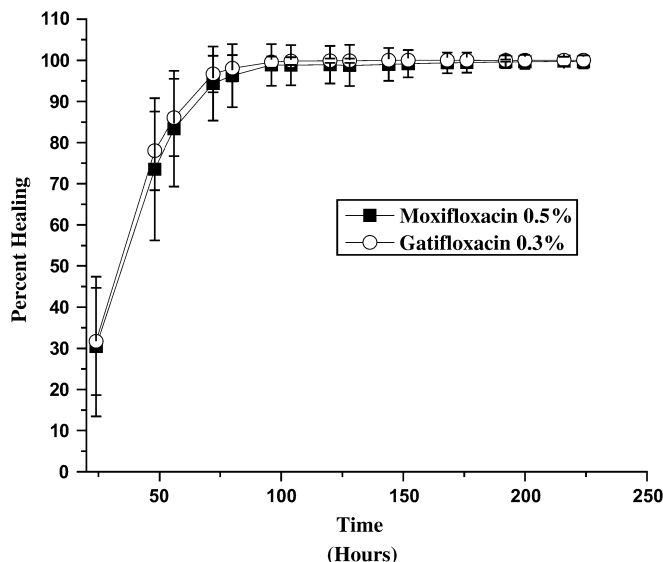
**RESULTS**

No significant differences were observed for the following variables between the 2 treatment groups in regard to age, sex ( $P = 1$ ), ethnicity ( $P = 0.6$ ), cycloplegic refraction, Schirmer test, or wound size at baseline (0 hours). A summary of baseline parameters is shown in Table 2.

Figure 1 shows a comparison of percent healing (mean  $\pm$  standard deviation) during the course of the study for moxifloxacin 0.5% and gatifloxacin 0.3% ophthalmic solutions. The mean healing times after PRK were similar for the moxifloxacin 0.5% group and for gatifloxacin 0.3%. The time

**TABLE 2. Baseline Parameters for Patients Undergoing Photorefractive Keratectomy**

Parameter	Moxifloxacin (n = 21, mean $\pm$ SD)	Gatifloxacin (n = 22, mean $\pm$ SD)	P
Age	33.38 $\pm$ 10.86	36.91 $\pm$ 12.58	0.33
Visual acuity OD	1.02 $\pm$ 0.54	1.25 $\pm$ 0.48	0.15
Visual acuity OS	1.03 $\pm$ 0.52	1.18 $\pm$ 0.54	0.36
Schirmer OD	10.86 $\pm$ 4.82	13.91 $\pm$ 7.71	0.13
Schirmer OS	12.57 $\pm$ 6.45	13.91 $\pm$ 6.44	0.50
Cycloplegic refraction OD	-3.35 $\pm$ 2.30	-3.47 $\pm$ 2.67	0.87
Cycloplegic refraction OS	-3.71 $\pm$ 2.15	-3.39 $\pm$ 2.60	0.65
Baseline wound size OD	65.63 $\pm$ 5.11	67.51 $\pm$ 5.14	0.25
Baseline wound size OS	64.89 $\pm$ 7.16	66.81 $\pm$ 5.70	0.36



**FIGURE 1.** A comparison of percent corneal healing (mean  $\pm$  standard deviation) after bilateral PRK. Moxifloxacin 0.5% and gatifloxacin 0.3% ophthalmic solutions were administered in both eyes immediately after surgery and then every 6 hours until complete wound healing had occurred.

to complete healing was similar for the 2 antibiotics: 87.8  $\pm$  19.9 hours for moxifloxacin 0.5% and 86.7  $\pm$  16.5 hours for gatifloxacin 0.3% ( $P = 0.79$ ). In addition, healing rates were approximately equivalent ( $P = 0.61$ ) for the 2 fluoroquinolones: moxifloxacin 0.78  $\pm$  0.18 mm<sup>2</sup> per hour and gatifloxacin 0.8  $\pm$  0.16 mm<sup>2</sup> per hour. No difference in postoperative uncorrected visual acuity ( $P > 0.67$ ) or haze ( $P > 0.09$ ) could be detected between the 2 groups 1 month after surgery.

**DISCUSSION**

Our laboratory conducted in vitro studies to compare the relative effects of 4 topical ophthalmic antibiotics: gatifloxacin 0.3% (Allergan), levofloxacin 0.5% (Quixin, Santen, Napa, CA), moxifloxacin 0.5% (Alcon), and ofloxacin 0.3% (Ocuflox, Allergan Inc.) on human corneal epithelial cells.<sup>5</sup> Each treatment group was exposed to 100  $\mu$ L of undiluted antibiotics or an artificial tear solution (Systane, Alcon Laboratories, Inc.) and evaluated after 5-minute exposure or 15-minute exposure. Live cells were evaluated using a Biotek FL600 Microplate Fluorescence Reader. Gatifloxacin, levofloxacin, and ofloxacin exhibited similar epithelial cell toxicity and showed a significantly greater percentage of cell death than moxifloxacin ( $P < 0.05$ ). These results suggested that there may be differences between the fluoroquinolone antibiotics in terms of wound healing of corneal ulcers, persistent epithelial defects, LASEK, or PRK.

Analogous to human corneas, the chicken cornea contains a prominent Bowman layer.<sup>6</sup> The relative corneal thickness contributed by the Bowman layer (1.3%) is similar to that reported for humans (1.7%). The chicken cornea has been deemed a more representative model of the human

cornea for reepithelialization studies than other animal models commonly used that lack a Bowman layer, and the adult chicken cornea is similar to the human cornea histologically.<sup>6,7</sup> We conducted photorefractive keratectomy experiments in the chicken model to compare balanced saline solution (BSS; Alcon Laboratories, Inc.), levofloxacin, moxifloxacin, and gatifloxacin. The antibiotics and the BSS were given 4 times per day until complete healing of the corneal epithelium had occurred. A slit-lamp camera was used to take pictures of the epithelial defect after surgery. Corneal wound healing rates after photorefractive keratectomy were similar among the BSS, levofloxacin, moxifloxacin, and gatifloxacin treatment groups. Moxifloxacin and gatifloxacin produced significantly smaller wound sizes than levofloxacin at 60 and 66 hours after surgery ( $P < 0.05$ ).

Published reports using animal models have measured the effects of topical fluoroquinolones on the ocular surface. Kovoor et al<sup>8</sup> conducted a rabbit study in which the animals were dosed 6 times on the first day of therapy and 4 times daily for the remaining 6 days of treatment. Moxifloxacin 0.5% did not produce any changes in epithelial thickness as measured by confocal microscopy, whereas gatifloxacin 0.3%, levofloxacin 0.5%, ofloxacin 0.3%, and ciprofloxacin 0.3% caused a small but significant ( $P < 0.05$ ) amount of corneal thinning. In a recent study using an intensive dosing protocol (1 drop of antibiotic every 5 minutes for 15 minutes followed by 1 drop every 15 minutes for 4 hours) that examined the effects of moxifloxacin and gatifloxacin on the rabbit corneal epithelium, Herrygers et al<sup>9</sup> reported no difference in mean corneal damage scores between gatifloxacin and moxifloxacin ( $P = 0.41$ ), gatifloxacin and control ( $P = 0.14$ ), or moxifloxacin and control ( $P = 0.23$ ). Drug penetration was shown in a rabbit model to be greater for moxifloxacin than gatifloxacin; however, the corneal permeability to carboxyfluorescein was 1.6 times lower, which suggests that moxifloxacin maintains better corneal integrity.<sup>10</sup> Superior corneal penetration of moxifloxacin is thought to be the result of the inherent characteristics of the molecule and not changes in the corneal epithelial tight junctions.

Donaldson and colleagues<sup>11</sup> conducted studies on the effects of moxifloxacin 0.5% ophthalmic solution on the cornea of normal human eyes by using confocal microscopy and slit-lamp biomicroscopy. The dosing regimen, which was similar to a therapeutic regimen used for patients undergoing cataract extraction, was 1 drop of moxifloxacin in 1 eye 4 times a day for 3 days. At the end of the treatment period, no significant differences in tear breakup time or visual acuity were observed between the study and contralateral control eyes ( $n = 15$  per group). Endothelial cell counts remained stable during the course of the 3-day study and were similar between the study and the untreated eyes. Epithelial cell counts were stable at visits 1 (baseline) and 2 (24 hours) and decreased similarly in the study and control groups visit 3 (72 hours). Nguyen et al<sup>12</sup> reported no difference between moxifloxacin 0.5% and gatifloxacin 0.3% on the basis of conjunctival injection, lid thickness, ocular surface sensation, pupil size, chemosis, or burning and stinging for normal patients dosed with 1 drop of antibiotic.

Durrie and Trattler<sup>13</sup> have examined the effects of moxifloxacin 0.5% and gatifloxacin 0.3% on corneal wound healing for LASIK and LASEK patients. No differences were found between the 2 antibiotics (administered 4 times per day) for several ophthalmic parameters, such as haze, edema, visual acuity, glare, halos, clarity of day or night vision, and dry eye symptoms, up to 1 week after surgery. No preference was noted by the patients between the 2 fluoroquinolones in terms of speed of recovery; irritation; redness; itching; gritty, sandy, or scratchy feeling; ease of use; overall vision; or overall comfort up to 7 days after LASIK surgery. The LASEK study examined the effects of 4-times-per-day dosing of moxifloxacin and gatifloxacin on corneal healing. There was no difference between a therapeutic regimen containing moxifloxacin and one containing gatifloxacin on the time to complete healing:  $5.5 \pm 0.2$  days for moxifloxacin and  $5.7 \pm 0.2$  days for gatifloxacin ( $n = 26$ ;  $P = 0.4903$ ).

These studies corroborate the work of others and demonstrate that the fluoroquinolones, moxifloxacin 0.5% and gatifloxacin 0.3%, are equivalent in terms of their corneal tolerability. At the time of initiation of this study we did not have a basis in the literature to form a sample size; however, Solomon et al<sup>14</sup> have recently shown a statistically significant difference in wound closure time in a smaller study with 20 PRK patients who were randomized to moxifloxacin or gatifloxacin. This finding suggests that our study was sufficiently powered to detect a significant difference in the time to complete wound healing.

Both compounds produced similar rates of corneal wound healing. Patients experienced similar degrees of corneal haze and levels of visual acuity. The results of this study suggest that moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% solution do not negatively affect the corneal wound healing process. Therefore, because of their broad spectrum of coverage, these antibiotics may have utility for patients undergoing photorefractive keratectomy.

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