# Early Addition of Topical Corticosteroids in the Treatment of Bacterial Keratitis

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## Abstract

**IMPORTANCE—**Scarring from bacterial keratitis remains a leading cause of visual loss.

**OBJECTIVE—**To determine whether topical corticosteroids are beneficial as an adjunctive therapy for bacterial keratitis if given early in the course of infection.

**DESIGN, SETTING, AND PARTICIPANTS—**The Steroids for Corneal Ulcers Trial (SCUT) was a randomized, double-masked, placebo-controlled trial that overall found no effect of adding topical corticosteroids to topical moxifloxacin hydrochloride in bacterial keratitis. Here, we assess the timing of administration of corticosteroids in a subgroup analysis of the SCUT. We define *earlier* administration of corticosteroids (vs placebo) as addition after 2 to 3 days of topical antibiotics and *later* as addition after 4 or more days of topical antibiotics.

**MAIN OUTCOMES AND MEASURES**—We assess the effect of topical corticosteroids (vs placebo) on 3-month best spectacle-corrected visual acuity in patients who received corticosteroids or placebo earlier vs later. Further analyses were performed for subgroups of patients with non-*Nocardia* keratitis and those with no topical antibiotic use before enrollment.

**RESULTS**—Patients treated with topical corticosteroids as adjunctive therapy within 2 to 3 days of antibiotic therapy had approximately 1-line better visual acuity at 3 months than did those given placebo (−0.11 logMAR; 95% CI, −0.20 to −0.02 logMAR; *P* = .01). In patients who had 4 or more days of antibiotic therapy before corticosteroid treatment, the effect was not significant; patients given corticosteroids had 1-line worse visual acuity at 3 months compared with those in the placebo group (0.10 logMAR; 95% CI, −0.02 to 0.23 logMAR; *P* = .14). Patients with non-*Nocardia* keratitis and those having no topical antibiotic use before the SCUT enrollment showed significant improvement in best spectacle-corrected visual acuity at 3 months if corticosteroids were administered earlier rather than later.

**CONCLUSIONS AND RELEVANCE**—There may be a benefit with adjunctive topical corticosteroids if application occurs earlier in the course of bacterial corneal ulcers.

When treating aerobic bacterial infections, the use of topical corticosteroids as an adjunctive therapy to topical antibiotics is still controversial among ophthalmologists.[1–5] A recent randomized clinical trial comparing corticosteroids with placebo as an adjunctive therapy found no difference in best spectacle-corrected visual acuity (BSCVA) at 3 months when all patients were analyzed.[6,7] The same trial found benefit with corticosteroid use in the subgroups with more severe ulcers (defined by enrollment visual acuity and the ulcer's size, depth, or location) and in BSCVA at 12 months among patients with ulcers caused by non-*Nocardia* species.[8,9] Some argue that the Steroids for Corneal Ulcers Trial (SCUT) started corticosteroid application too late in the course of the ulcer and that an overall difference would have been seen if corticosteroids had been started earlier.[1] Enrolled SCUT patients were treated with antibiotics before corticosteroid or placebo use anywhere between 2 and 34 days. A longer duration of topical antibiotic treatment before corticosteroid or placebo administration was due to enrollment procedures or topical antibiotic treatment given before enrolling in the SCUT. Here, we use results to determine if the duration of topical antibiotic treatment before adding topical corticosteroids is a predictor of combined corticosteroid-antibiotic success.

## Methods

### Trial Methods

The SCUT was a randomized, double-masked, placebo-controlled trial assessing the effect of adjunctive topical corticosteroid treatment on outcomes in bacterial keratitis in patients at 2 US centers and 1 center in India.[6,7] Of the 500 patients included in SCUT, 8 were excluded from the analysis because of missing data specifying the duration of antibiotic treatment before receiving the corticosteroid or placebo. On presentation, screened patients with corneal ulcers were immediately treated with moxifloxacin hydrochloride every hour while awake for the first 48 hours, then every 2 hours until enrolled in the study. Patients were enrolled in the trial within 2 to 6 days after screening if their bacterial culture result was positive. Here, we compare BSCVA at 3 months in patients with earlier (2–3days) vs

later (4 or more days) addition of topical corticosteroids or placebo using a multiple linear regression model. We further assess treatment effect in patients with severe, moderate, and mild ulcers using prespecified SCUT baseline BSCVA subgroups (severe, 1.7 logMAR [counting fingers]; moderate, 0.3–1.6 logMAR [20/40 to 20/800]; and mild, <0.03 logMAR [<20/40]). In addition, we compare BSCVA at 3 months between earlier and later administration of corticosteroids or placebo in patients with non-*Nocardia* keratitis and those who did not receive preenrollment antibiotics. Variation in the duration of antibiotics in the patients having no topical antibiotic use before SCUT enrollment was due to study enrollment procedures requiring a culture-positive bacteria specimen.

### Statistical Analysis

Baseline characteristics of patients with an earlier vs a later addition of corticosteroids or placebo were compared using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Three-month BSCVA was assessed using a multiple linear regression model, including study treatment (corticosteroids vs placebo), timing of administering the corticosteroids or placebo (2–3 days vs 4 or more days), and an interaction term of study treatment by administration timing. In addition, we corrected for enrollment acuity in the model by using orthogonal third-degree polynomials to minimize the squared error of prediction. The same model structure was used in all subgroups. Comparison of baseline BSCVA was analyzed using the Wilcoxon rank sum test.

Sensitivity analyses of the model were performed by controlling for *Nocardia* species, duration of symptoms, and scar size and imputing missing data for duration of antibiotic treatment for 8 patients. Additional analyses included using a different dichotomous threshold (2 days [earlier administration] vs 3 or more days [later administration]) and duration of antibiotics as a continuous predictive term. All *P* values were 2-sided. All analyses were performed using Stata, version 10.0 (StataCorp LP).

#### Ethics

The University of California, San Francisco; Dartmouth Medical School; and the Aravind Eye Care System granted institutional review board approval. This study conformed to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants.

## Results

Most patients received corticosteroids or placebo after 2 days of topical antibiotics (214 of 500 [42.8%]), followed by 3 days (126 of 500 [25.2%]) and 4 or more days (152 of 500 [30.4%]) (Table 1). Baseline characteristics between patients with an earlier vs a later addition of corticosteroids or placebo were largely balanced (Table 2). We found a significantly higher proportion of male to female patients (*P* = .01), a longer duration of symptoms (*P* = .01), a larger infiltrate scar size (*P* = .06), and a higher proportion of *Nocardia* vs non-*Nocardia* species (*P* < .001) in the group of patients who received corticosteroid or placebo administration later.

Results of the multiple linear regression model, including treatment arm, earlier vs later addition of corticosteroids or placebo, and the interaction term of treatment arm by time of administration, are shown in Table 3. The interaction term was significant ($P = .01$), indicating the effect of the treatment may depend on the time of administration. In patients who received corticosteroids or placebo earlier, corticosteroid use was associated with a −0.11 logMAR BSCVA improvement (n = 311; 95% CI, −0.20 to −0.02; $P = .01$) compared with those in the placebo group. In patients given corticosteroids or placebo later, the effect was not significant; corticosteroid-treated patients had 1-line worse visual acuity than did the placebo-treated patients (n = 139; 0.10 logMAR; 95% CI, −0.02 to 0.23; $P = .14$). Baseline BSCVA in earlier vs later administration of corticosteroids or placebo was not different ($P = .62$). Adding covariates that were significantly different at baseline did not alter the association, including sex, duration of symptoms before presentation, *Nocardia* vs non-*Nocardia* species, and scar size.

In patients with severe ulcers, corticosteroid therapy produced approximately a 3-line improvement in visual acuity compared with those given a placebo if administered within 2 to 3 days (n = 85; −0.27 logMAR; 95% CI, −0.50 to −0.04; $P = .02$). Of the patients in this category who were given corticosteroids or placebo later, those in the corticosteroid group showed a 2-line improvement in visual acuity, although this was not significant (n = 40; −0.24 logMAR; 95% CI, −0.59 to 0.10; $P = .17$). When corticosteroids or placebo were administered earlier in patients with moderately severe ulcers, those receiving corticosteroid therapy demonstrated a 1-line improvement in visual acuity compared with those given placebo (n = 165; −0.09 logMAR; 95% CI, −0.20 to 0.01; $P = .09$). Conversely, later administration of treatment showed that the corticosteroid-treated group performed approximately 2 lines worse than did the placebo group (n = 72; 0.20 logMAR; 95% CI, 0.04 to 0.36; $P = .01$). In patients with mild ulcers, there was no difference shown in those treated earlier (n = 61; 0.02 log-MAR; 95% CI, −0.09 to 0.13; $P = .70$). However, those who had corticosteroid treatment later had a 2-line worse visual acuity than those given placebo (n = 27; 0.19 logMAR; 95% CI, 0.02 to 0.36; $P = .03$).

Of the 450 patients who had a 3-month BSCVA, 400 had ulcers with non-*Nocardia* keratitis, of whom 289 received corticosteroids or placebo within 2 to 3 days while the remaining 111 were given corticosteroids or placebo within a mean (SD) of 5.8 (3.9) days (range, 4–33 days). The patients with earlier administration showed 1.3 logMAR lines of improvement at 3 months with corticosteroid treatment than those given placebo (n = 289; 95% CI, −0.22 to −0.03 logMAR; $P = .01$), whereas the later administration showed no difference in corticosteroid effect (n = 111; 0.06 logMAR; 95% CI, −0.09 to 0.20 logMAR; $P = .45$).

More than two-thirds of the patients (n = 335) reported no use of ocular antibiotics before enrolling in the trial. Once enrolled, the mean (SD) duration of moxifloxacin (the study antibiotic) was 2.5 (0.8) days (range, 2–6 days). The patients having no preenrollment antibiotic treatment reported approximately 2 fewer days of symptoms than those who had pretreatment, with a mean of 6.4 vs 8.1 days ($P = .09$). Baseline BSCVA in those having no preenrollment antibiotic treatment was not different from those who had antibiotic pretreatment ($P = .70$). Using multiple linear regression correcting for baseline BSCVA and including the interaction term, the model showed that corticosteroid-treated patients

performed 1.2 lines better than did placebo-treated patients (n = 279; –0.12 logMAR; 95% CI, –0.21 to –0.04; *P* = .02) if treatment was administered earlier and showed no significant effect if administered later (n = 28; 0.21 logMAR; 95% CI, –0.06 to 0.48; *P* = .13).

For 8 patients receiving antibiotics, the duration of antibiotic treatment was not captured. Assuming that the duration of antibiotic treatment was the same as the duration of symptoms produced similar results. Changing the dichotomous categories of earlier vs later administration of corticosteroids or placebo to 2 vs 3 or more days did not substantially alter the results (–0.12 logMAR; 95% CI, –0.23 to –0.03; *P* = .04). A continuous variable for duration of antibiotics (days) in the multiple linear regression model for all patients was a significant predictor, showing 1 line of vision loss for every 5 days of corticosteroid or placebo delay (0.02 logMAR; 95% CI, 0.01 to 0.03; *P* = .002).

## Discussion

The SCUT was a large 500-patient randomized clinical trial that did not show an overall difference in 3-month visual acuity with adjunctive corticosteroids in bacterial keratitis.[6,7] A potential limitation to the SCUT may have been that corticosteroids or placebo were not administered early enough to show a difference across all degrees of ulcer severity.[1,10] Approximately one-third of SCUT patients received topical antibiotics for longer than 4 days before corticosteroid or placebo administration. In the remaining two-thirds who were given corticosteroids or placebo within 2 to 3 days of initiation of antibiotic therapy, corticosteroids provided benefit over placebo regardless of sex, infiltrate scar size, duration of symptoms, and *Nocardia* vs non-*Nocardia* species. Within the subgroups of severe, moderate, and mild ulcers, patients receiving corticosteroids fared better when treatment was given earlier, demonstrating no evidence effect modification caused by ulcer severity.

Although not significant, the analysis demonstrated that patients who received later administration of treatment showed improvement with placebo vs corticosteroids. We believe this is due to the imbalance of patients with *Nocardia* keratitis having a longer duration of antibiotic use before treatment administration. Patients with *Nocardia* keratitis should be differentiated from those with other bacteria. In SCUT, corticosteroids were detrimental in patients with *Nocardia* keratitis.[9,11,12] Here, when we removed patients with *Nocardia* keratitis from the multiple linear regression model, corticosteroids were beneficial when administered earlier and neutral when administered later.

To further assess the hypothesis that antibiotic-corticosteroid success may be contingent on earlier application, we looked at the subset of patients with no topical antibiotic treatment before presentation. Exposure to antibiotics was more controlled within this group (2–6 days). These 335 patients sought treatment earlier in the course of their infection, reporting approximately 1.7 fewer days of symptoms on average. There was no difference in BSCVA between the pretreated patients and those who were not treated before enrollment. This subgroup showed 1.2 lines of improvement in visual acuity with corticosteroids over placebo if administration occurred earlier.

Comparing baseline characteristics revealed a higher proportion of men to women in the group with the longer duration of antibiotics before corticosteroid or placebo administration. Sex difference was not due to those treated with antibiotics before presentation, which was equally balanced between men and women. Longer duration of symptoms, larger infiltrate scar size, and higher proportion of *Nocardia* vs non-*Nocardia* species were found in the group of patients who received 4 or more days of antibiotics before corticosteroid or placebo administration. These baseline imbalances suggest that the patients who were not healing sought tertiary care later. Analyses controlling for these characteristics did not substantially change the results.

## Conclusions

We show evidence that earlier application of corticosteroid therapy could be a predictor of combined corticosteroid-antibiotic success in bacterial keratitis. Further subgroup analysis was unable to demonstrate an effect modification by ulcer severity or confounding by time to presentation. Because this was a non-prespecified subgroup analysis and the overall results of the original SCUT were null, subgroup results presented here should be considered with caution.[13] It is important to recognize that in SCUT, all cases of bacterial keratitis were confirmed by positive cultures, and these results are not relevant if the diagnosis is uncertain.[14] Corticosteroid use has been shown to be associated with worse outcomes in keratitis caused by fungus and *Acanthamoeba*.[15,16] This report demonstrates that microbiology culture results can be obtained early enough to gain visual benefit from topical corticosteroids. Despite effects across subgroups, not all subgroups were prespecified, and thus changes in clinical practice are not yet recommended.[17] A randomized clinical trial based on Gram stain rather than bacterial culture results, as well as screening for preenrollment antibiotic treatment, is needed to confirm the possibility that earlier administration of corticosteroids as an adjunctive therapy to antibiotics improves visual acuity outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**Table 1**

Counts for 500 Patients Shown by Duration of Antibiotic Use Before Corticosteroid or Placebo Administration

| Duration of Antibiotic Use Before Corticosteroid or Placebo Administration, d | Patients for Each Duration, No. (%) |
|---|---|
| 2 | 214 (42.8) |
| 3 | 126 (25.2) |
| 4 | 52 (10.4) |
| 5 | 41 (8.2) |
| 6 | 22 (4.4) |
| 7–14 | 27 (5.4) |
| 15–21 | 4 (0.8) |
| 22–32 | 6 (1.2) |
| Not reported | 8 (1.6) |

**Table 2**

Baseline Data for 492 Patients Treated With Corticosteroids or Placebo Earlier (2–3 d) vs Later ( 4 d)[a]

| Characteristic | Earlier Addition of Corticosteroids or Placebo | Later Addition of Corticosteroids or Placebo | *P* Value |
|---|---|---|---|
| No. of patients | 340 (69.1) | 152 (30.9) | <.001 |
| No. of days of topical antibiotics before addition of corticosteroid or placebo, median (IQR) | 2 (2–3) | 5 (4–6) | <.001 |
| Treatment allocation | | | |
|   Placebo | 172 (50.6) | 74 (48.7) | .77 |
|   Corticosteroid | 168 (49.4) | 78 (51.3) | |
| Sex | | | .01 |
|   Male | 172 (50.6) | 96 (63.2) | |
|   Female | 168 (49.4) | 56 (36.8) | |
| Age, median (IQR), y | 54.5 (40–62) | 51 (40–61) | .33 |
| Duration of symptoms, median (IQR), d | 4 (3–7) | 5 (3–8) | .01 |
| Cornea depth, % | | | .50 |
|   >0–33 | 160 (47.1) | 61 (40.1) | |
|   >33–67 | 99 (29.1) | 49 (32.2) | |
|   >67–100 | 81 (23.8) | 42 (27.6) | |
| Scar size, median (IQR), mm | 2.54 (1.86–4.00) | 3.09 (2.09–4.22) | .06 |
| Epithelial defect, median (IQR), mm | 1.73 (1.00–3.04) | 1.98 (1.05–3.26) | .12 |
| Ulcer location | | | .16 |
|   Entirely in periphery | 52 (15.3) | 15 (10.0) | |
|   Partially covering 4-mm circumference | 216 (63.5) | 96 (63.2) | |
|   Completely fills 4-mm circumference | 71 (20.9) | 40 (26.3) | |
| Visual acuity, median (IQR), logMAR | 0.75 (0.36–1.70) | 0.90 (0.38–1.70) | .61 |
| Organism | | | |
|   *Nocardia* species | 24 (7.1) | 29 (19.1) | <.001 |
|   Non-*Nocardia* species | 316 (92.9) | 121 (79.6) | |

Abbreviation: IQR, interquartile range.

[a]Values are given as number (percentage) unless otherwise indicated.

## Table 3

Multiple Linear Regression Predicting 3-Month BSCVA Correcting for Baseline Visual Acuity and Using Covariates

| All Cases With 3-mo Visit | Coefficient (95% CI), logMAR | P Value |
|---|---|---|
| Treatment arm (corticosteroid vs placebo) | 0.10 (−0.3 to 0.23) | .14 |
| Earlier vs later administration of corticosteroid or placebo | −0.02 (−0.13 to 0.10) | .78 |
| Interaction between treatment arm and administration time | −0.21 (−0.37 to −0.05) | .01 |

Abbreviation: BSCVA, best spectacle-corrected visual acuity.