# Chlorhexidine Gluconate 0.02% as Adjunct to Primary Treatment for Corneal Bacterial Ulcers

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**ABSTRACT:** **Background:** It is common practice to use topical antiseptic formulations prior to specific therapy in superficial infections and injuries, but not in corneal bacterial ulcers. There is accumulating evidence proving chlorhexidine gluconate 0.02%, an antiseptic agent, as an effective treatment for infectious keratitis.

**Objectives:** To investigate the safety and efficacy of chlorhexidine gluconate 0.02% as an adjunct therapy for corneal bacterial ulcers.

**Methods:** Twenty-six patients with corneal bacterial ulcers were treated with standard empirical antibiotic treatment. The study group was treated with chlorhexidine gluconate 0.02% while controls received placebo for one week. The patients were followed for at least 1 month.

**Results:** No allergic or toxic reactions were noted. Although a higher baseline severity of ulcers existed in the study group, no differences were found in final vision, scarring extent, or recovery duration.

**Conclusions:** Chlorhexidine gluconate 0.02% may improve the clinical course of corneal ulcers.

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**KEY WORDS:** cornea, ulcer, chlorhexidine, antiseptic agents

Bacterial ulcers, a potentially sight-threatening condition, are defined as inflammatory infiltrates of the corneal stroma with an epithelial defect resulting from an infection from one or more bacterial species [1]. In the developing world it is a major cause of blindness [2] and a serious cause of ocular morbidity worldwide. Bacterial corneal ulcers generally follow a traumatic break in the corneal epithelium, thereby providing an entry for bacteria. The traumatic episode may be minor, such as a minute abrasion from a small foreign body, or it may result from such causes as tear insufficiency, malnutrition, contact lens use, or surface diseases such as corneal edema and erosions. Corneal and external disease specialists have published extensive recommendations for the evaluation and treatment of corneal infections. The current gold standard of therapy involves culturing areas suspicious for infection before initiating empiric antibiotic treatment [3]. Then, based on laboratory findings and the clinical response to the empiric therapy, specific antibacterial treatment can replace or supplement the current therapy.

Empiric treatment of corneal infections requires a broad-spectrum antibiotic while waiting for microbial culture results [4]. The use of general antiseptics, or specifically chlorhexidine gluconate, provides further broad-spectrum coverage. Chlorhexidine gluconate exerts its effect by disrupting bacterial membrane function. It has a proven effect against Acanthamoeba [5-9], a range of gram-positive and gram-negative bacteria [10-12], viruses [13,14] and fungi [15,16], and is also considered effective against *Chlamydia trachomatis* [17].

Chlorhexidine gluconate has little non-specific binding to corneal tissues, allowing high drug availability [18]. It has many potential advantages over the currently available antibiotics, including broader antibacterial coverage, reduced degree of bacterial resistance, and much lower cost. Furthermore, clinically, chlorhexidine gluconate 0.02% has minimal corneal epithelial toxicity. *In vitro* bathing of epithelial and endothelial surfaces of rabbit corneas with 0.05% chlorhexidine gluconate in Ringer saline caused swelling of the corneal stroma [19]. At a concentration of 0.2%, it is toxic to the skin, conjunctiva and corneal epithelial cells and corneal fibroblasts, but at a concentration of 0.02% it appears safe for most cells [20]. In mammals, 0.02% concentration of chlorhexidine exerted no apparent ocular toxicity [21].

It is common practice to use topical antiseptic formulations prior to any other specific therapy [22,23] in superficial infections and injuries. There is accumulating evidence proving chlorhexidine as an effective treatment for fungal [15,16] and amoebic [5-9] keratitis, but there are few data in the current literature regarding its effectiveness for corneal bacterial ulcers. Bu et al. [24] evaluated the use of topical chlorhexidine for experimental bacterial keratitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* in rabbits. They concluded that short-term topical chlorhexidine treatment was effective, when compared with ciprofloxacin and tobramycin/cefazolin, particularly for *S. aureus*.

The purpose of the present study was to investigate the safety and efficacy of chlorhexidine gluconate 0.02% as an adjunct to primary therapy for corneal bacterial ulcers in humans.

## PATIENTS AND METHODS

This double-blind, randomized, placebo-controlled prospective study was performed in accordance with the Declaration of Helsinki. Before initiation of the study, all the subjects were given an information sheet regarding the content and purpose of the study. Twenty-eight patients (28 eyes) clinically diagnosed with corneal ulcers that fulfilled the inclusion criteria were recruited at the Ophthalmology Department of Meir Medical Center, Kfar Saba, Israel.

Patients enrolled in the study were at least 18 years of age and were clinically diagnosed as having an acute corneal bacterial ulcer in one eye. The remarkable differences in presentation among bacterial, viral and fungal corneal ulcers allow presumptive diagnosis. None of the patients had been treated for the infection before enrollment, nor did they have known allergies to the study medications. After signing an informed consent, all patients were treated according to the study protocol and were followed for at least 4 weeks.

Exclusion criteria included best corrected visual acuity < 6/60 in the fellow eye, corneal impending perforation or true perforation, clinical suspicion of infectious agents other than bacteria, or other underlying ocular diseases causing visual loss. Patients with peripheral ulcers and with rheumatoid arthritis were excluded from the study. Patients unwilling to participate fully or to complete follow-up visits were not eligible.

At baseline evaluation, age and gender were recorded, as well as the general health status, chronic diseases, systemic medications (with specific attention to immune-suppressive drugs) and known allergies. Assessment of ophthalmic diseases included history of corneal infections, along with history of ocular treatments. In order to evaluate the risk factors for corneal infection, the patients were specifically asked about contact lens wear, history of eye trauma and ocular foreign bodies, chronic ophthalmic surface diseases, and use of contaminated ocular medications or solutions. The patient's symptoms were recorded with a full description of their characteristics and duration.

Physical examinations included BCVA, measured with the Snellen chart under standardized conditions, and then transformed into LogMAR. Intraocular pressure was measured using the calibrated Goldman applanation tonometer. Complete biomicroscopic examination was performed, with special attention to eyelid and cornea status, injection of the conjunctiva, and staining. Anterior chamber involvement was assessed with attention to cells, which were graded from 0 to +4 (0 = no inflammatory cells, trace = < 5 cells, +1 = 5–10 cells, +2 = 10–20 cells, +3 = 20–30 cells, +4 = cells too numerous to count). The degree of hypopyon and flare was also graded from 0 to 4.

Ulcer evaluation included measurements of its minimum and maximum diameters in millimeters, with evaluation and grading of the depth of stromal invasion (1 = subepithelial, 2 = < ¼ stromal thickness, 3 = < ½ stromal thickness, 4 = < ¾ stromal thickness, and 5 = full thickness). Epithelial defects were measured in millimeters and any presence of satellite infiltrates was recorded. Corneal photography was performed using a Nikon Coolpix 4500 camera at baseline and at the third and fifth study visits.

Each patient underwent corneal scrapings using a sterile mini-blade for smear and cultures. The specimens were examined microscopically as a wet mount in 10% potassium hydroxide and as a heat-fixated mount with Gram stain. Corneal scrapings were cultured at 28°C in Sabouraud's dextrose agar, chocolate agar, and blood agar media. If there was no growth after 14 days the cultures were discarded.

Patients were randomly assigned: 14 to the treatment group (A) and 14 to the control group (B), according to a randomization chart prepared by the hospital pharmacy prior to the beginning of the study. Group A received treatment from bottle A, which was chlorhexidine gluconate 0.02% (Seton healthcare group, Oldham OL1 3HS, UK) diluted in sterile buffered diluent for injection (DEMO S.A. Pharmaceutical industries, Greece). Identical-appearing bottle B contained placebo drops, which was the same sterile buffered diluent. The drops were installed six times a day during the first 7 days of treatment, and then stopped at once. The bottles were prepared, kept at -4°C, and randomly assigned to one of the two study arms by the hospital pharmacist; hence, the investigator was blind as to its content.

All the patients were also treated with the standard empirical treatment for bacterial keratitis: fortified cefazolin 50 mg/ml and fortified gentamicin 14 mg/ml. After a loading regimen of one drop of each treatment every 15 minutes in the first hour, the drops were installed once an hour during the first 48 hours, with at least 5 minute intervals between the two drops. The antibiotics were slowly tapered according to the patient's clinical response. The investigators were allowed to add topical steroids and cycloplegics according to their clinical judgment. This empiric treatment could be changed, according to the laboratory results and clinical course. The investigator was instructed to stop the study medication whenever it was suspected of causing an allergic or toxic reaction.

Follow-up examinations were conducted by two investigators (N.G. and G.N.). On day 0, a full baseline evaluation was done and treatment with the standard antibiotics plus drops A or B was started. The five follow-up visits took place on day 2 (± 1), day 5 (± 2), day 11 (± 2), day 18 (± 2) and day 28 (± 2). At each visit the clinical response was monitored, and BCVA and IOP were measured. The investigators measured the maximal and minimal dimensions of the infiltrate and

BCVA = best corrected visual acuity

IOP = intraocular pressure

the epithelial defect. They also recorded the appearance of satellites, corneal edema, endothelial inflammatory plaque, and corneal scarring. The anterior chamber inflammation, including cells and flare when present, was graded according to the standard grading system. The investigators monitored the type and frequency of topical treatment and each patient was asked about their symptoms in each study visit. After the first month, the patients were followed until complete healing was noted. Complete healing was defined as complete epithelial restoration, infiltrate elimination, absorption of corneal edema, and clearance of the anterior chamber.

### STATISTICAL ANALYSIS

Categorical variables were compared with Fisher exact, or chi-square exact tests as appropriate; continuous variables were compared with unpaired *t*-tests. *P* values < 0.05 were considered statistically significant.

## RESULTS

Twenty-eight patients (28 eyes) were enrolled and randomly assigned to the two groups. One patient in the control group was lost to follow-up 2 days after enrollment and one patient in the control group withdrew his consent to participate in the study on the first day due to personal reasons. The results of the remaining 26 patients were analyzed.

There were no statistically significant differences between the two groups in terms of age (mean age 38.68 years, range 22–70), gender (13 males, 13 females), or chronic systemic diseases.

**Table 1.** Baseline data: symptoms and signs of study patients

| Symptoms and signs | | Group A | Group B | Total | *P-Fisher's* exact test |
|---|---|---|---|---|---|
| Photophobia | No. | 3 | 4 | 7 | 1.000 |
| | % | 21.4 | 33.3 | 26.9 | |
| Reported visual loss | No. | 3 | 3 | 6 | 1.000 |
| | % | 21.4 | 25 | 23.1 | |
| Foreign body sensation | No. | 5 | 5 | 10 | 1.000 |
| | % | 35.7 | 41.7 | 38.5 | |
| Pain | No. | 5 | 5 | 10 | 1.000 |
| | % | 35.7 | 41.7 | 38.5 | |
| Tearing | No. | 7 | 9 | 16 | 0.248 |
| | % | 50.0 | 75.0 | 61.5 | |
| Conjunctival congestion | No. | 14 | 12 | 26 | 1.000 |
| | % | 100.0% | 100.0 | 100.0 | |
| Discharge | No. | 1 | 0 | 1 | 1.000 |
| | % | 7.1% | 0.0 | 3.8 | |
| Eyelid edema | No. | 4 | 3 | 7 | 1.000 |
| | % | 28.6% | 25.0 | 26.9 | |

Comparing the patient's records regarding past corneal infections in the study eye reveals that one eye (7.1%) in group A and two eyes (16.7%) in group B had a history of corneal infections ($P = 0.580$). There was one past event of corneal infection in the fellow eye in both groups (7.1% in group A and 8.3% in group B, $P = 1.000$). No significant differences between the two groups were found in the risk factors for corneal infections ($P = 0.391$). Five patients in each group had contact lens-related ulcers (35.7% in group A and 41.7% in group B, $P = 1.000$). Besides corneal infections or refractive errors, the patients had no other ophthalmic pathologies.

### BASELINE EVALUATION

There were no significant differences in patients' symptoms or signs [Table 1] at baseline. BCVA (LogMAR) at baseline was 0.21 ± 0.27 in group A and 0.14 ± 0.30 in group B ($P = 0.557$). No significant differences were found in the IOP at baseline (mean IOP 11.5 ± 2.8 mmHg).

### ULCER EVALUATION AT BASELINE

- *Ulcer mean length*: 1.31 ± 0.70 mm in group A and 0.72 ± 0.61 mm in group B ($P = 0.033$).
- *Ulcer mean width:* 0.923 ± 0.624 mm and 0.542 ± 0.462 mm in group A and B, respectively. Although this difference did not reach statistical significance ($P = 0.098$), most ulcers in the study group were wider than the controls.
- *Ulcer depth:* In both groups, the ulcer depth ranged from grade 2 to 4. There were no full thickness (grade 5) ulcers in either group. There were no statistically significant differences in the average ulcer depth at baseline between the two groups ($P = 0.104$). Nevertheless, when analyzing the deeper ulcers separately, there were significantly more grade 4 ulcers in the study group compared to none in the control group ($P = 0.042$).
- *Satellite infiltrates:* Six patients (42.9%) in group A and 7 (58.3%) in group B had satellite infiltrates at baseline ($P = 0.695$).
- *Epithelial defects:* All the patients in both groups had epithelial defects at baseline, but no statistically significant differences were noted between the sizes of the defects ($P = 0.795$).
- *Anterior chamber reaction (cells/flare):* Three patients in both groups (21.4% and 25.0% in groups A and B, respectively) had either flare or cells in the anterior chamber.

### EVALUATION AT STUDY VISITS

The compliance to follow-up was high, with no statistically significant exceptions between the two groups. All patients were treated according to the study protocol with no known compliance issues.

The analysis of patients' symptoms shows no significant differences between the two groups during follow-up examina-

**Table 2.** Follow-up data: BCVA, ulcers dimensions, and presence of epithelial defects

| Study visit | Group | Mean BCVA LogMAR | *P* value | Mean ulcer length (mm) | *P* value | Mean ulcer width (mm) | *P* value | Epithelial defects | *P-Fisher's* exact test |
|---|---|---|---|---|---|---|---|---|---|
| Baseline | A | 0.21 | 0.557 | 1.31 | 0.033** | 0.923 | 0.098* | 100% | |
| | B | 0.14 | | 0.72 | | 0.542 | | 100% | |
| Visit 1 | A | 0.16 | 0.545 | 1.29 | 0.054* | 0.736 | 0.235 | 93% | 0.580 |
| | B | 0.24 | | 0.60 | | 0.475 | | 83% | |
| Visit 2 | A | 0.12 | 0.573 | 1.04 | 0.120 | 0.679 | 0.254 | 57% | 1.000 |
| | B | 0.10 | | 0.56 | | 0.417 | | 58% | |
| Visit 3 | A | 0.10 | 0.640 | 1.10 | 0.124 | 0.564 | 0.295 | 64% | 0.238 |
| | B | 0.14 | | 0.35 | | 0.309 | | 33% | |
| Visit 4 | A | 0.09 | 0.059* | 0.66 | 0.411 | 0.131 | 0.586 | 7% | 1.000 |
| | B | 0.03 | | 0.21 | | 0.210 | | 10% | |
| Visit 5 | A | 0.08 | 0.799 | 0.00 | | 0.000 | | 0% | 0.580 |
| | B | 0.06 | | 0.00 | | 0.000 | | 0% | |

* Borders statistical significance
** Statistically significant

tions. When comparing the signs of infection along the follow-up visits, a significant reduction in eyelid edema and congestion was found in group A (treated with chlorhexidine gluconate 0.02%) on day 2 (± 3) of the follow-up visit ($P = 0.014$), which disappeared during subsequent follow-up examinations. There were no other significant differences in patients' signs.

No significant difference was noticed in patients' visual acuity or IOP. At the fourth visit, the mean BCVA in group A was better than in group B and nearly reached statistical significance ($P = 0.059$). This difference disappeared on subsequent visits [Table 2].

A comparison of the ulcer dimensions reveals that although the mean dimensions at baseline, both length and width, were higher in the study group, those differences disappeared during follow-up visits [Table 2]. The infiltrates resolved after a similar period. No differences were noted in the presence and extent of epithelial defects between the two groups, both at baseline and during follow-up visits [Table 2]. When comparing the infiltrate depths, although there were significantly more deep infiltrates graded as grade 4 in the study group at baseline, no differences were recorded in any of the follow-up visits.

The density of the infiltrates was gradually reduced at similar rates along the follow-up examinations in both groups. This was also true regarding satellite infiltrates and anterior chamber reaction. All lesions were cured during the 1 month follow-up. A similar number of corneal scars was recorded in both groups: 10 patients (71.4%) in the study group versus 8 patients (66.7%) in the control group ($P = 1.000$).

Cultures were positive in 19 of the 26 cases (69%). The identified pathogens are listed in Table 3. All of the pathogens were sensitive to cefazolin and/or gentamicin. No significant differences were found in the number and type of identified bacteria between the two groups.

## DISCUSSION

Topical antiseptic formulations containing single active ingredients such as alcohol, iodine or chlorhexidine gluconate are recognized by the U.S. Food and Drug Administration as "generally safe and effective for preparation of the skin prior to surgery" or "prior to an injection" and include "catheter care, ostomy hygiene, intravenous site preparation," etc. (Federal Register, 1994). Using antiseptic formulation prior to any other therapy is common practice procedure in medicine for many kinds of superficial infections and injuries. Antiseptic agents are commonly used before ophthalmic procedures and surgeries [16,23] as prophylactic treatment.

Our assumption was that using the chlorhexidine gluconate 0.02%, which is an established and relatively safe therapy,

**Table 3.** Identified bacteria

| Pathogens | No. |
|---|---|
| *Pseudomonas aeruginosa* | 6 |
| *Staphylococcus* coagulase negative | 4 |
| *Staphylococcus aureus* | 2 |
| *Klebsiella pneumoniae* | 1 |
| *Providencia stuartii* | 1 |
| *Serratia liquefaciens* | 1 |
| *Enterobacter cloacae* | 1 |
| *Serratia marcescens* | 1 |

as an adjunct therapy for corneal bacterial ulcer can improve the clinical course and prognosis with minimal toxicity. Our findings showed that chlorhexidine gluconate 0.02% was safe and did not cause allergic or toxic reactions. There was less eyelid edema and congestion in the study treatment group at the first follow-up examination on day 2 (± 1). This finding was despite the fact that both ulcer length and depth at baseline were significantly greater in that group. Although there were significantly more infiltrates graded as grade 4 in the study group at baseline, this difference disappeared later on and no differences between the lesion depths were recorded in any of the follow-up visits.

We believe that the evidence for our basic assumption in this study is not firm owing to the small number of cases and the relatively small size and low severity of the ulcers in the random group of patients. This may be related to the fact that one of the inclusion criteria stipulated that only non-treated ulcers be included in the study. This criterion resulted in inclusion of early ulcers that are typically smaller and not severe. Further investigation of the safety and efficacy of chlorhexidine gluconate 0.02% as an adjunct therapy for corneal bacterial ulcers is required. This treatment might be especially beneficial in other settings, since this inexpensive, broad microbicidal spectrum antiseptic agent may serve as a practical treatment.

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**"Did God have a mother?" Children, when told that God made the heavens and the earth, innocently ask whether God had a mother. This deceptively simple question has stumped the elders of the church and embarrassed the finest theologians, precipitating some of the thorniest theological debates over the centuries. All the great religions have elaborate mythologies surrounding the divine act of Creation, but none of them adequately confronts the logical paradoxes inherent in the question that even children ask"**

Michio Kaku (b. 1947), American theoretical physicist and futurist