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# Efficacy and Safety of Mercuric Oxide in the Treatment of Bacterial Blepharitis

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**A double-masked, placebo-controlled, randomized study was done to assess the safety and clinical and quantitative microbiologic efficacy of 1% mercuric oxide (yellow) ophthalmic ointment in the treatment of eyelid infections, i.e., bacterial blepharitis. A total of 39 patients with bacterial counts and clinical signs indicative of eyelid infection were treated twice daily for 7 days. Clinical biomicroscopic examination and quantitative microbiologic cultures were done just prior to initiation of treatment and again on days 3 and 7. Statistical analysis revealed a significant improvement in the clinical signs, bacterial count, cure rate, and improvement rate for subjects taking the active medication, compared with those taking the placebo on days 3 and 7. In addition, the medication was well tolerated.**

Mercuric oxide (yellow) is an antibacterial agent which has been incorporated into an ointment base for ophthalmic use in the treatment of common minor eyelid infections. It has been available in this form without prescription for over 30 years. It is antibacterial by its ability to reversibly inhibit bacterial sulfhydryl enzymes (5). Side effects, other than minor local irritation experienced by some individuals upon initial application, are rare with short-term use. Reports of local hypersensitivity reactions resulting in reversible blepharitis and conjunctivitis have also been rare (10). Rarely, continuous long-term use has resulted in bluish gray discoloration of the eyelids, conjunctiva, and peripheral cornea, without irritation or disturbance of visual acuity (20).

Bacterial blepharitis is a common minor infection of the eyelid margin and is an indication for treatment with an antibacterial agent such as mercuric oxide. The safety and efficacy of 1% mercuric oxide ophthalmic ointment in the treatment of minor eyelid infections have been addressed in one report in the literature (9). That study concluded that the medication was safe and effective in reducing the number of bacteria in subjects with blepharitis or styes. This study was designed to assess the effects of 1% yellow mercuric oxide ophthalmic ointment on clinical signs and symptoms of blepharitis as well as the safety and quantitative microbiologic efficacy of the ointment.

## MATERIALS AND METHODS

**Preliminary study.** A preliminary study was done to assess the number and type of bacteria present as normal base-line flora of the eyelid margin in this geographic area. The purpose of this study was to establish guidelines for what would be quantitatively considered microbiologically abnormal. These guidelines would improve the sensitivity of the study for detecting a treatment effect, if one existed. Any inadequacy of these guidelines would result in less of a difference in the response rate between the treatment and control groups. Cultures of the lower eyelid margin were taken from both eyes of 10 subjects who were determined by biomicroscopy to be free of eyelid infection. The culture and processing techniques are described below. From the preliminary study we derived the normal range of the bacterial count (mean ± two standard deviations). Only persons with an initial bacterial count two standard deviations above the normal range were included in the primary study.

**Primary study.** The drug evaluation study was designed to be randomized, placebo controlled, and double masked. The test medication was 1% yellow mercuric oxide ophthalmic ointment (Stye; Commerce Drug Co., Farmingdale, N.Y.). The placebo was the anhydrous ointment base without the active ingredient. The placebo ointment was similar in color to the ointment containing active agent, so patients were unaware of which treatment they received. Patients who had biomicroscopic evidence of blepharitis but no other inflammatory pathology of the eye and who were microbiologically eligible as noted above were enrolled in the primary study. These patients had not used any topical medication in the preceding 72 h. Each patient was advised of the nature of the study and signed an informed consent form. Other information obtained included the age, sex, and race of the subject and the date of onset of the present episode, the number of episodes in the past year, the date of most recent therapy, and any concomitant medications.

A clinical examination was performed when the patients were enrolled in the study (day 1) and on study days 3 and 7. At the initial exam and each follow-up exam, the cornea, anterior chamber, iris, lens, and visual acuity were also evaluated and bacterial cultures of the eyelid margins were taken. In addition, a biomicroscopic evaluation was performed to assess the degree of blepharitis. The blepharitis was graded on a scale of 0 to 4+: 0, no blepharitis; 1+, erythema of the eyelid margin; 2+, erythema and either exudation or fibrinous scaling; 3+, erythema, exudation or fibrinous scaling, and edema; and 4+, erythema, exudation or fibrinous scaling, edema, and ulceration.

Improvement in the signs was considered to be any decrease in severity of the eyelid disease after the time of enrollment. Cure of the signs was defined as elimination (to a value of 0) of any clinical findings present at the time of enrollment.

Each patient was given a tube of randomly coded ointment and taught the method of application to the eyelid margin twice daily. No ointment was to be used on the morning of the day of the follow-up examination, so that the bacterial cultures would not be affected by the incorporation of any

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ointment. Compliance was ensured by interviewing the patient and examining the amount of ointment remaining in the tubes at each return visit.

**Bacterial culture procedure.** Cultures from the lower eyelid margin of each affected eye were obtained by using techniques routinely employed in our laboratory (6). A sterile calcium alginate swab was moistened in brain heart infusion broth. One surface of the swab was rubbed firmly across the eyelid margin at the base of the lashes from the nasal margin to the temporal margin and back. The same surface of the swab was streaked directly to a blood agar plate (Columbia agar with 5% sheep blood). The plates were incubated at 37°C in an atmosphere containing 5 to 10% carbon dioxide for 24 h. The number of colonies of each bacterial type was counted by using magnification and an electronic colony counter. The organisms were identified by using standard bacteriologic techniques. The identification of staphylococci was based on the coagulase test and mannitol fermentation.

**Statistical analysis.** The Wilcoxon rank sum test (16) was used to test the difference between the treatment and control groups in ordinal variables (e.g., age, bacterial count, and degree of blepharitis). A modification of the Wilcoxon rank sum test (12) was used to compare the clinical scores on a given day of treatment after adjusting for another variable, e.g., the severity of the signs of blepharitis on day 1. To perform the modified test, the adjusting variable is divided into categories. Within each category, a rank sum test is performed, and the results of these rank sum tests are then pooled.

Statistical comparisons of treatment and control groups for differences in binary variables (e.g., sex and cure rate) were performed by using the chi-square test for 2 × 2 contingency tables without correcting for continuity. Because of small sample sizes, Fisher's exact test was used to compare treatment and control groups for improvement in symptoms.

## RESULTS

**Preliminary study.** In the preliminary study to assess base-line normal flora, *Staphylococcus epidermidis* grew from all eyelids cultured and was the only organism isolated from this group. The average number of colonies was 52 ± 28.5 (± standard deviation). By using these data, it was prospectively determined that only subjects with initial colony counts of 110 or greater (two standard deviations above the mean) would be eligible for inclusion in the primary study evaluation.

**Primary study patient population.** A total of 58 subjects were enrolled in the drug evaluation study. Of these, 19 were excluded from the primary study evaluation. The reasons for exclusion were: low initial bacterial counts (six subjects), noncompliance (five subjects), lack of follow-up examination (five subjects), and adverse reactions (three subjects). Minor adverse reactions included two subjects with probable allergic reactions and one subject who complained of transient burning. The three subjects who did not complete the study because of adverse reactions were all in the active treatment group. The number of subjects withdrawn from the study because of noncompliance or lack of follow-up examination was the same for the treatment and control groups. Therefore, it is unlikely that these reasons for withdrawal masked adverse effects on additional subjects. There were no significant differences in age, sex, race, or duration of disease between excluded and included subjects.

A total of 39 subjects were eligible for the study by the criteria reviewed above. Random assignment placed 19 of these subjects in the active treatment group and 20 in the placebo group. The placebo group had a slightly greater value for clinical score prior to treatment, but the difference was not statistically significant ($P > 0.10$). The differences between groups in initial bacterial count, duration of symptoms, and sex and race were small and not statistically significant (Table 1). Subjects in the placebo group tended to be older than subjects in the active treatment group ($P = 0.06$). For this reason, subsequent analyses were adjusted by age in three age groups: group 1, younger than 35, group 2, 35 to 64, and group 3, 65 and older.

TABLE 1. Baseline variables[a]

| Treatment | No. of subjects/total | | Age (yr) | Initial colony count | Initial clinical score |
|---|---|---|---|---|---|
| | Males | Symptoms >30 days[b] | | | |
| Placebo | 7/20 | 4/19 | 57.0 ± 20.6 | 473.0 ± 260.5 | 2.5 ± 0.89 |
| Active agent | 6/19 | 6/18 | 46.4 ± 21.2 | 440.5 ± 200 | 2.1 ± 0.97 |

[a] $P$ values (obtained from 2 × 2 contingency tables for the first two comparisons and the Wilcoxon rank sum test for the remainder) were not significant for any variable, except age ($P = 0.06$). Value ± standard deviation.

[b] Duration of symptoms was used as an ordinal variable in significance testing.

**Microbiologic evaluation.** In 92% (17 of 19 active and 19 of 20 placebo) of the cases, *S. epidermidis* was the organism recovered in the largest numbers and was considered the etiologic agent. Two subjects in the active group and one in the placebo group had *Staphylococcus aureus* as the etiologic agent; the two subjects in the active group also had concomitant *S. epidermidis*, but in small numbers. Other organisms, present in small numbers, were recovered from both groups. Nine subjects in the active group and eight subjects in the placebo group had mixed cultures. In the active group, the other organisms recovered included: *Bacillus* spp. (three subjects), alpha-hemolytic *Streptococcus* spp. (two subjects), *Branhamella catarrhalis* (one subject), *Corynebacterium* spp. (four subjects), *Moraxella* sp. (one subject), and *Acinetobacter* sp. (one subject). These organisms were eradicated by day 7, with the exception of the *Acinetobacter* sp. and the alpha-hemolytic *Streptococcus* sp. (in one case), both of which were reduced in number but not eliminated. One patient had the appearance of saprophytic *Neisseria* sp., *Bacillus* sp., and *Micrococcus* sp. on day 3, but none were present on day 7. Concomitant organisms in the placebo group were: *Corynebacterium* spp. (two subjects), *Citrobacter* sp. (one subject), *S. aureus* (one subject), alpha-hemolytic *Streptococcus* sp. (one subject), and *Penicillium* sp. (one subject). The *Penicillium* sp., alpha-hemolytic *Streptococcus* sp., and *Corynebacterium* sp. (in one case) were eliminated by day 7. The *Citrobacter* sp. and remaining *Corynebacterium* sp. were reduced in number but not eliminated, and the *S. aureus* persisted. As with the active medication group, there were bacteria in the placebo group not present on initial culture which appeared on day 3. These included *Corynebacterium* spp. (two subjects), *S. aureus* (two subjects), and *Citrobacter* sp. (one subject). The *Citrobacter* sp. and *Corynebacterium* sp. (one subject) were eliminated by day 7, while the remaining *Corynebacterium* sp. and both cases with *S. aureus* persisted. Two subjects in the placebo group had the appearance of *Corynebacterium* sp. on day 7 which was not present

TABLE 2. Status of infection after follow-up treatment

| Treatment | Colony count[a] | | Clinical score[b] | | No. of patients with signs | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Cured | | Improved | |
| | Day 3 | Day 7 | Day 3 | Day 7 | Day 3[c] | Day 7[d] | Day 3[e] | Day 7[f] |
| Placebo ($n$ = 20) | 473 ± 246 | 560 ± 425 | 1.74 ± 1.0 | 1.25 ± 1.3 | 0 | 6 | 11 | 14 |
| Active agent ($n$ = 19) | 47 ± 82 | 106 ± 194 | 0.84 ± 0.8 | 0.37 ± 0.8 | 7 | 14 | 16 | 18 |

[a] $P$ for both days <0.0005 (derived by using the Wilcoxon rank sum test). Value ± standard deviation.
[b] $P$ for both days = 0.005 (derived by using the Wilcoxon rank sum test). Value ± standard deviation.
[c] $P$ = 0.008 (derived by using Fisher's exact test).
[d] $P$ = 0.007 (derived by using the chi-square test for 2 × 2 contingency tables).
[e] $P$ = 0.048 (derived by using the chi-square test for 2 × 2 contingency tables).
[f] $P$ = 0.044 (derived by using the chi-square test for 2 × 2 contingency tables).

on prior cultures. Little significance was attached to these concomitant organisms, since they were present in small numbers and were either eradicated by the active ointment or appeared to be transient in most cases. These organisms were not included in the statistical analysis.

The results of significance testing for microbiologic status after treatment are presented in Table 2. The bacterial counts for the active treatment group were significantly lower than those for the control group on both day 3 and day 7 at the $P < 0.001$ level.

**Clinical evaluation.** The results of significance testing for comparing the clinical status of the active treatment and placebo groups are presented in Table 2. The clinical status significantly differed by day 3 ($P < 0.01$). The $P$ value for this difference remained less than 0.01 after adjusting for age or for clinical score prior to treatment. On day 7 the $P$ value was 0.005 and was unchanged after adjusting for initial clinical score or age.

Also shown in Table 2 is a second analysis of the effects of treatment on clinical signs compared with the effects on cure rates of the treatment and placebo groups. On day 3, there were no subjects in the placebo group who were cured, and there were seven subjects in the treatment group who were cured ($P$ = 0.01 by Fisher's exact test). Three of the cured subjects were age 60 or older, and the cured subjects tended to be older than the subjects who were not cured (although the difference was not statistically significant). Therefore, it is unlikely that the older age of the placebo subjects contributed to a lower cure rate for this group.

On day 7, the $P$ value for cure rates was 0.007 by the chi-square test. All seven treated subjects who were age 60 or older were cured of clinical signs by day 7, again suggesting that the older age of the placebo group was not a contributing factor to the lower cure rate for this group.

In the group receiving the active medication, 16 (84%) of 19 had an improvement in the signs of lid disease by day 3 and 18 (95%) of 19 had an improvement by day 7. In the placebo group, 11 (55%) of 20 had improved clinically by day 3 and 14 (70%) of 20 had improved by day 7. The emollient effect of the placebo ointment base was probably responsible for the clinical effects seen in that group. The cornea, anterior chamber, iris, lens, and visual acuity were also evaluated clinically but were not noted to change, with the exception of persistent punctate epithelial erosion in the cornea of one subject (placebo), punctate epithelial erosion which resolved by day 3 in two subjects (one placebo and one active), the presence of a small peripheral infiltrate on day 7 in one case (placebo), and persistent micropannus in one case (placebo).

Most placebo subjects improved without treatment, although they were not cured. The improvement rate was significantly lower for placebo subjects than for treated subjects.

Nine subjects in the placebo group and 10 subjects in the active group reported minor side effects. These side effects were transitory, lasting from several minutes to a day, and included a mild to severe burning sensation, light sensitivity, tearing, and red eye. Examination of the eyes in question did not reveal any significant pathology of the cornea or conjunctiva.

## DISCUSSION

The older literature generally refers to *S. aureus* as the causative agent in bacterial blepharitis (1, 17, 18); however, more recently, the pathogenic properties and causative role of the coagulase-negative staphylococci have been recognized (2–4, 7, 8, 11, 13, 14, 19). Although generally regarded as normal endogenous microflora, *S. epidermidis* has been implicated as the causative agent of blepharitis in 50, 69, and 86% of cases in three series (9, 13, 19). It was also the organism most frequently recovered (92% of cases) in large numbers from the blepharitis subjects in this study. The exact mechanisms by which *S. epidermidis* organisms produce the characteristic eyelid margin inflammation have not been completely determined. Reports suggest that plasmid- and chromosome-mediated multiple-antibiotic resistance (3, 11) or the ability to anaerobically ferment mannitol (19) may be associated with more pathogenic strains. Subconjunctival injection in rabbits of a cell filtrate of some *S. epidermidis* strains isolated from the eyelid margins of blepharitis patients has produced a purulent conjunctivitis of significantly greater severity than isolates from normal eyelid margins (19). In addition, some of these strains were found to produce a dermonecrotizing toxin which is typically associated with *S. aureus* and absent from *S. epidermidis* strains isolated from normal eyelid margins. The production of enzymes which act upon lipids, esters, and fatty acids has been associated with *S. epidermidis* strains isolated from patients with chronic blepharitis (3). These enzymes are thought to break down some components of meibomian gland secretions, resulting in the production of substances which are irritative to the eyelids and conjunctiva. It is likely that, because of the intrinsic properties of some strains, colonization of the eyelid margins by these organisms is adequate to cause blepharitis (7). However, it has also been noted that many colonies are usually recovered from eyelid cultures from blepharitis patients, and although quantitative data have not been reported, the severity of the condition has been associated with the number of bacteria present (15). If this is the case, exacerbations may be induced by increasing the numbers of organisms by contiguous spread from

adjacent skin, nasal mucosa, meibomian glands, etc., which harbor the organism or by contact with contaminated hands or makeup (15).

Staphylococcal blepharitis is a chronic condition with periods of exacerbation and remission. It is usually kept under control by a regimen of eyelid hygiene, with application of an antibacterial ointment for episodes of exacerbation. Hygiene consist of cleansing the eyelid margins with a diluted solution of a mild shampoo. Hot compresses and lid massage are sometimes recommended as adjuncts. An antibiotic ointment, such as erythromycin or bacitracin, is often prescribed when patients have active episodes. An antibacterial ointment such as 1% yellow mercuric oxide ophthalmic ointment which is available over-the-counter allows blepharitis patients to treat active episodes without the need to obtain a prescription. Yellow mercuric oxide (1%) ophthalmic ointment is recommended for use twice daily, and patients are cautioned to consult a physician if the condition worsens or persists after 1 week of treatment. It is recommended for the short-term treatment of blepharitis and not for long-term topical therapy.

To evaluate the safety and clinical and microbiologic efficacy of 1% yellow mercuric oxide ophthalmic ointment, subjects in this study were treated twice daily for 7 days with either the ointment containing the active medication or the placebo ointment base. Statistical analysis of the clinical signs showed a significant improvement in the clinical scores of subjects receiving the active medication on treatment days 3 and 7, compared with those of placebo controls. Some placebo subjects also showed improvement in clinical signs. This effect may be due to the emollient properties of the ointment base.

Statistical analysis of symptoms showed no significant differences in efficacy between active drug and placebo in cure of symptoms on day 3 (1 of 18 versus 1 of 19 cured) or day 7 (4 of 18 versus 9 of 19 cured; $P = 0.11$). The symptoms of blepharitis are usually trivial, however, with the main complaint usually being the cosmetically troublesome objective sign of red eyelids. Also, symptoms of blepharitis are a less-reliable outcome measure to evaluate objectively than signs.

Statistically, bacterial counts were significantly reduced in the active group compared with the placebo group. This difference was evident on days 3 and 7 of treatment. A similar finding of microbiologic efficacy has been reported by other investigators (9).

The medication was well tolerated by the study subjects. Complaints of short-term irritation, burning, and tearing upon application of the ointment were reported by both groups. These symptoms are considered nonspecific and may be described by patients with active bacterial blepharitis even when not being treated.

In summary, we have shown that 1% yellow mercuric oxide ophthalmic ointment is safe and effective, both clinically and microbiologically, in improving the clinical signs in patients with bacterial blepharitis. This medication offers an alternative which is safe for the treatment of common minor eyelid infections and convenient for the patient, since it is available without prescription.

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