Topical Steroids in Bacterial Keratitis: A Retrospective Study

ABSTRACT

Purpose: To review the outcomes, risk factors and morbidity of bacterial keratitis treated with and without topical steroids.

Design: Retrospective cohort study.

Methods: Demographics, risk factors, culture results, ulcer characteristics, and timing to epithelialization, visual acuity and recurrences were recorded. Patients were classified into 2 groups: 1. Topical antibiotics/steroids (ASG), and 2. Antibiotics only group (AOG).

Results: Seventy-two eyes were identified. Thirty-seven were classified in the ASG and 35 in the AOG. Predisposing factors were identified in 87.5% of cases. Penetrating keratoplasty, previous surgery, contact lens wear and Herpes simplex keratitis were the most common overall. Microorganisms were identified in 85.5% and 60% of ASG and AOG, respectively. Epithelialization was completed at a mean 17.62 and 16.06 days in ASG and AOG, respectively (p= 0.533). Final mean BSCVA was 1.59±1.07 and 1.64±1.21 log MAR in ASG and AOG, respectively (p= 0.864). The number of gained Snellen lines was 0.13±0.22 in ASG and 0.14±.0.24 in AOG (p = 0.860). There were no recurrences.

Conclusion: Although a non-statistical significant delay in re-epithelialization was noted in the ASG, this did not translate into a statistical difference in final BSCVA, gained Snellen lines or recurrence of infection. In this serie, adjuvant topical steroids were not associated with an increase in unfavorable outcomes.

Key words: Bacterial keratitis, corneal ulcer, topical corticosteroids, treatment of corneal ulcers, treatment of bacterial keratitis.

Resumen

Objetivo: Analizar la morbilidad, factores de riesgo y resultados asociados al tratamiento de queratitis bacteriana con y sin el uso de esteroides tópicos.

Diseño: Estudio de cohortes retrospectivo.

Métodos: Se analizaron los datos demográficos, factores de riesgo, características de la úlcera, tiempo de re-epitelización, agudeza visual y recurrencias en pacientes con queratitis bacteriana. Los pacientes fueron clasificados en dos grupos: 1. Antibióticos/esteroide tópicos (ASG) y 2. Únicamente antibióticos (AOG).

Resultados: Se identificaron 72 ojos, de los cuales 37 fueron clasificados en el ASG y 35 en el AOG. Encontramos por lo menos un factor de riesgo en el 87.5% de los casos; siendo los más comunes la queratoplastia penetrante, cirugía ocular previa, uso de lente de contacto y queratitis por Herpes simplex. Los cultivos lograron identificar un agente causal en el 85.5% y en el 60% del ASG y AOG, respectivamente. El epitelio cerró por completo en un promedio de 17.62 y 16.06 días en ASG y AOG, respectivamente (p= 0.533). En promedio, la agudeza visual corregida al fin del estudio fue de 1.59±1.07 y 1.64±1.21 log-MAR en ASG y AOG, respectivamente (p= 0.864). En promedio el ASG ganó 0.13±0.22 líneas en la carta de Snellen, mientras que el AOG ganó 0.14±0.24 (p = 0.860). No hubo casos recurrentes.

Conclusión: Aunque la re-epitelización fue un poco más lenta en el ASG, la diferencia no fue estadísticamente significativa ni se tradujo en cambios significativos en la agudeza visual corregida, el número de líneas ganadas en la carta de Snellen o el número de recurrencias. En esta serie, adyuvante encontramos que el uso adyuvante de esteroides tópicos no fue asociado con resultados desfavorables.
**INTRODUCTION**

Bacterial keratitis is a potential sight-threatening disease, responsible for up to 20% of the world’s blindness. Globally, more than 1 million people are visually disabled because of microbial corneal infection.

Topical corticosteroids have an unclear role in the management of bacterial keratitis. The reasoning behind corticosteroids as an adjuvant in treating bacterial keratitis is the idea that they may help resolve corneal inflammation, facilitate epithelial and stromal healing and minimize corneal opacification, neovascularization, and destruction; on the other hand, steroids can potentiate microbial replication, promote recrudescence, slow recovery, accelerate stromal loss and increase the risk of perforation. Host reactions account for much of the edematous, infiltrative, and necrotizing changes seen in bacterial keratitis, which may cause progressive corneal damage.

There is evidence that the use of topical corticosteroids without an antibiotic has a deleterious effect on experimental models of bacterial keratitis, and that their use for other reasons before the occurrence of bacterial keratitis more than triple the risk of subsequent complications including treatment failure, progressive infection, and perforation.

A meta-analysis of retrospective studies on steroid use in bacterial keratitis from 1950 to 2000 concluded that the efficacy of topical corticosteroids is unproven. There are two published prospective trials on the subject with no definitive evidence to support or discourage their use.

The goal of this study was to retrospectively evaluate the outcomes of bacterial keratitis when treated with topical antibiotic therapy with or without adjunctive topical steroids at our center in the last 5 years by examining the speed of epithelial healing, final visual acuity, gained visual acuity and recurrence rate.

**METHODS**

We retrospectively reviewed the electronic medical records of patients hospitalized with the diagnosis of bacterial keratitis at the Department of Ophthalmology, Hadassah-Hebrew University Medical Center in the last 5 years. All data collection for the study was made according to local legislation and in accordance with the principles of the Declaration of Helsinki.

The following data was collected for each patient: age, gender, affected eye, ocular history, predisposing risk factors, presenting and final visual acuity (UCVA), best spectacle corrected visual acuity (BSCVA), culture results, topical steroid use, ulcer characteristics such as size and location, healing time and recurrences. It is important to mention that at our institution all cases of moderate/severe bacterial keratitis are admitted and treated as in-patients, with daily follow-up thus allowing us to have daily information on the evolution of these cases.

A corneal ulcer was defined as a corneal epithelial defect associated with an underlying acute suppurative infiltrate in the stroma, and showing variable endothelial or anterior chamber reaction, diffuse bulbar and/or limbal injection, chemosis, discharge, lid edema, severe pain and photophobia.

Location (central or paracentral) and size of ulcer at presentation were evaluated. Ulcers were defined as small when measuring less than 4 mm², medium between 4 and 16 mm² and large when measuring more than 16 mm². Only medium and large size corneal ulcers were included in the study.

Ulcers were scraped and inoculated into blood, chocolate and Sabouraud’s dextrose agar, thioglycate broth as well as smears for Gram and Giemsa stains before treatment was initiated. Our microbiology laboratory analyzed all samples.

We retrospectively classified patients in 2 groups, according to the treatment received:

- **Antibiotic+Steroid Group (ASG):** patients with bacterial keratitis, who received adjunctive topical steroids (dexamethasone phosphate 0.1% drops) to the standard antibiotics regime.
- **Antibiotic-only Group (AOG):** patients with bacterial keratitis, who received standard therapy with topical antibiotics.

The criteria for topical dexamethasone phosphate 0.1% application were:

1. They should be introduced at least 48 hours after treatment with antibiotics was initiated.
2. Identification of microorganism with antibiotic sensitivity results.
3. Clinical improvement when no microorganism was identified.

Dexamethasone phosphate 0.1% was applied 2 to 6 times a day, never exceeding the topical antibiotic dosage and was usually stopped before discontinuation of antibiotic treatment with the exception of ulcers on penetrating keratoplasty (PKP) or when the treating physician considered it necessary to decrease scarring.

The standard topical antibiotic treatment protocol was a combination of cefazolin 5% and gentamicin 1.4% drops every hour for the first two days, to be tapered according to clinical response down to a minimum of 4 times a day and then discontinued. Antibiotic the-
rapy was modified on the basis of cultures, antibacterial susceptibility and clinical response.

An ulcer was considered healed when the epithelial defect was closed with no staining on fluorescein dye application, and antibiotic treatment was continued at least 4 times a day for a week after the ulcer healed.

Recurrence of infection was defined as a reappearance of abscess occurring within one week of full re-epithelialization, when the infective element was considered cleared\(^ resemblance{20}\), while late re-infections were defined as new infections occurring more than 30 days after initial infection and more than a week after full epithelialization.

Time to complete epithelialization, final UCVA, BSCVA gained VA and recurrence rate were the study’s main outcome measures.

Two tailed T-Test and Chi-Square Test were used for statistical analysis using SPSS software version 11.0 (SPSS Inc, Chicago, Ill, USA). All reported P values are two-tailed. P < 0.05 was considered statistically significant.

Exclusion criteria included small ulcer size or marginal location, original active non-bacterial infection with microbial super infection, those treated not according to protocol or that started treatment before admission, patients that were pre-treated with steroids (except cases after PKP), neurotrophic ulcers, and those associated with an autoimmune condition. We also excluded cases in which corneal scrapings were not performed, and patients who presented with corneal perforation or endophthalmitis.

**RESULTS**

Seventy-two eyes of 72 patients were found to be eligible. Thirty-seven eyes were allocated in the ASG and 35 eyes in the AOG. The demographic characteristics of the patients are displayed in Table 1. The mean age was 52.5 ± 22.24 (ranging from 13 to 92 years) in ASG and 59.8 ± 23.2 (from 14 to 91 years) in AOG (P = 0.178).

At presentation, the range of BCVA was similar in both groups; mean BSCVA was 2.20± 0.91 log MAR (Snellen equivalent, 0.07±0.19) and 2.14 ± 1.03 log MAR (Snellen equivalent, 0.07±0.13) in ASG and AOG respectively (P=0.801) (Table 1).

Almost 40% of ulcers in the study were large (37.8% in ASG and 40% in AOG) and more than half of them localized centrally (56.8% in ASG and 62.9% in AOG). The size of the ulcers and their location are summarized in Table 3.
coccus species (25% and 23.8% respectively). More than one type of bacteria was found in 12.5% and 14.3% of the cultures in ASG and AOG, respectively.

Topical steroid treatment was initiated between days 3 and 16 (mean 6.88 ± 4.14 days) and applied for a mean period of 45.2 ± 29.79 days. Seventy three percent of the patients were started on topical steroid 4 times a day. Steroid therapy was gradually tapered and stopped according to the clinical picture.

Corneal epithelialization was complete between 5 and 45 days (mean 17.62 ± 10.78 days) in ASG and 3 to 38 days (mean, 16.06 ± 9.71 days) in AOG. The difference was not statistically significant (p = 0.533) (Table 4).

Final mean BSCVA was 1.59 ± 1.07 log MAR (Snellen equivalent, 0.20 ± 0.91) in ASG and 1.64 ± 1.21 log MAR (Snellen equivalent, 0.22 ± 0.29) in AOG (p = 0.864). The number of gained Snellen lines was 0.13 ± 0.22 in ASG and 0.14 ± 0.24 in AOG; this difference was not statistically significant (p = 0.860) (Table 4).

No recurrence of bacterial keratitis was noted during the study (Table 4). Late re-infections, all of them more than 30 days after initial infection and more than a week after full epithelialization were noted in five patients receiving topical steroids and only in two patients receiving exclusively antibiotic treatment (Table 5).

### DISCUSSION

In the present study, both groups were similar with respect to age, gender, visual acuity at presentation, and ulcer characteristics such as size and location. Forty percent of the patients had large sized ulcers and 60% of them were located centrally, most of them also had poor visual acuity on admission, reflecting the high incidence of severe ulcers. Predisposing risk factors were identified in 87.5% of the patients. PKP, CL and previous ocular surgery being the most common risk factors in the ASG and previous ocular surgery; HSK and PKP in the AOG. Our results in this regard are similar to previous published studies, in which such predisposing factors have been identified in 84% to 97% of patients with suppurative keratitis.10,14,15

PKP was the predominant risk factor in the study, especially among older patients and was present in 42% of late re-infections. Bacterial keratitis after PKP is a serious complication resulting in graft failure and poor visual outcomes. Patients who have undergone PKP are at increased risk for bacterial keratitis because of graft hyposthesia, long term use of topical corticosteroids, soft contact lens wear, persistent epithelial defects, exposed sutures, ocular surface disorders and lid abnormalities.16-21 Although there are no prospective studies demonstrating an ideal topical corticosteroid dosage for long term rejection prevention after PKP, a survey by Price et al22 on steroid usage patterns during and after low risk penetrating keratoplasty showed that 46% and 22% of surgeons would continue low dose topical steroids indefinitely for pseudophakic and phakic patients, respectively, to avoid rejection, thus confirming that an important number of surgeons consider that the risks of bacterial keratitis and other complications due to chronic steroid therapy are offset by the perceived benefit of protection against immunological graft rejection.

In this retrospective study, steroid treatment was associated with a delay in re-epithelialization that was not statistically significant. Two published trials on this topic have found a trend towards improved outcomes with steroids,

### Table 4. Comparative outcomes.

<table>
<thead>
<tr>
<th></th>
<th>ASG</th>
<th>AOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to full epithelialization</td>
<td>17.62 ± 10.78 days</td>
<td>16.06 ± 9.71 days</td>
</tr>
<tr>
<td>Final mean BSCVA (Log Mar)</td>
<td>1.59 ± 0.07</td>
<td>1.64 ± 1.21</td>
</tr>
<tr>
<td>Gained Snellen lines</td>
<td>0.13 ± 0.22</td>
<td>0.14 ± 0.24</td>
</tr>
<tr>
<td>Recurrences</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Legend: Antibiotic + steroid group (ASG); Antibiotic only group (AOG).

### Table 5 Cases with late re-infections.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs) / Gender</th>
<th>Associated conditions</th>
<th>Culture 1</th>
<th>Culture 2</th>
<th>Time to re-infection (days)</th>
<th>BCVA At presentation</th>
<th>BCVA At re-infection</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>86/M</td>
<td>PKP</td>
<td>PA</td>
<td>Str.vrd</td>
<td>34</td>
<td>Fs50cm</td>
<td>HM</td>
<td>PKP</td>
</tr>
<tr>
<td>2*</td>
<td>20/F</td>
<td>Cl</td>
<td>PA</td>
<td>Staph.sp</td>
<td>30</td>
<td>HM</td>
<td>HM</td>
<td>PKP</td>
</tr>
<tr>
<td>3</td>
<td>70/F</td>
<td>PBK</td>
<td>Poly-bacterial</td>
<td>Poly-bacterial</td>
<td>120</td>
<td>Fs30cm</td>
<td>Fs20cm</td>
<td>PKP</td>
</tr>
<tr>
<td>4</td>
<td>49/M</td>
<td>PKP</td>
<td>PA</td>
<td>PA</td>
<td>150</td>
<td>HM</td>
<td>Fs40cm</td>
<td>PKP</td>
</tr>
<tr>
<td>5</td>
<td>61/F</td>
<td>PKP</td>
<td>Str.pnm</td>
<td>NG</td>
<td>44</td>
<td>Fs30cm</td>
<td>HM</td>
<td>Failed graft</td>
</tr>
<tr>
<td>6</td>
<td>90/F</td>
<td>Neg</td>
<td>Str.pnm</td>
<td>NG</td>
<td>54</td>
<td>HM</td>
<td>HM</td>
<td>Refuses PKP</td>
</tr>
<tr>
<td>7*</td>
<td>77/f</td>
<td>Cl, PBK</td>
<td>Staph.sp</td>
<td>NG</td>
<td>51</td>
<td>Fs1m</td>
<td>HM</td>
<td>Waiting for PKP</td>
</tr>
</tbody>
</table>

* Patient not on steroid treatment, * Second recurrence developed 47 days after the first one. PA was the isolated microorganism in the second recurrence. Penetrating Keratoplasty (PKP), contact lens (Cl), pseudophakic bullous keratopathy (PBK), Pseudomonas aeruginosa (PA), Streptococcus pneumoniae (Str.pnm), Staphylococcus species (Staph.sp), no growth (NG).
while their results on epithelialization differ. One of the studies found a statistically significant delay on the group receiving the steroids, while this difference was not significant in the other.\textsuperscript{11,12} Moreover, we agree with Sirinivasan et al that re-epithelialization is not an optimal outcome measure when the intervention, steroids in this case, may cause a delay in healing time while still translating to better VA and reduced infiltrate/scar size.\textsuperscript{12} Although re-epithelialization is an important goal, we should focus on more clinically relevant outcomes such as gained Snellen lines and final VA. The other outcome measures for the present study: final mean BSCVA, number of gained Snellen lines and the number of recurrences, were similar in both groups and we did not find any statistical significant difference.

Five out of 7 cases with late re-infection were on topical steroid treatment when the re-infection occurred. This is consistent with previous studies that suggest topical steroid use significantly predisposes eyes with pre-existing corneal disease to ulcerative keratitis and once microbial keratitis occurs, prior corticosteroid use significantly increases the odds of antibiotic treatment failure or other infectious complications.\textsuperscript{3} In our series, 5 out of these 7 patients had to be treated with a PKP one of which failed. Another patient is waiting for a graft and another one refused to have a PKP despite our recommendation. It is interesting that the 2 patients that were not on steroid treatment at the time of re-infection, had the shortest interval between the primary infection and the re-infection (30 and 34 days), and that the cases on steroids presented much later between 44 and 150 days post infection.

In our retrospective cohort study, adjunctive topical steroid use for the treatment of bacterial keratitis did not seem to statistically affect re-epithelialization or final BSCVA and did not increase the number of recurrent infections; thus, at least in our patient population, steroid treatment did not appear to be associated with an increase in adverse effects.

Due to the limitations of our study, we could not demonstrate any benefit or detriment of adding corticosteroids to the antibiotic regime. Recently, a large randomized control trial (SCUT)\textsuperscript{22} concluded that there was no overall difference in 3-month BSCVA when using adjunctive corticosteroid therapy, as well as no safety concerns with its use. Our findings are in accordance with these results. Another interesting finding from this study is that they found a significant positive effect in final BSCVA of corticosteroid use in subgroups with BSCVA at baseline worse than counting fingers and in those with ulcers that were completely central, demonstrating that steroids might still be useful in some cases.

In conclusion, steroids were not associated with an increase in adverse events in our series, and although a non-statistical significant delay in re-epithelialization was noted, this did not translate into a significant difference in final BSCVA, gained Snellen lines or recurrence of infection.

REFERENCES