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Topical corticosteroids as adjunctive therapy for bacterial keratitis

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Abstract

Background—Bacterial keratitis is a serious ocular infectious disease that can lead to severe visual disability. Risk factors for bacterial corneal infection include contact lens wear, ocular surface disease, corneal trauma and previous ocular or eyelid surgery. Topical antibiotics constitute the mainstay of treatment in cases of bacterial keratitis where as the use of topical

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*Indicates the major publication for the study

Contributions of Authors: Conceiving the review: OS, RSC

Designing the review: OS, JMGR

Coordinating the review: OS, JMGR, SSV

Data collection for the review

-Designing electronic search strategies: Cochrane Eyes and Vision Group editorial base

-Undertaking manual searches: OS, JMGR, SH:

-Screening search results: OS, RSC, SH

-Organising retrieval of papers: OS, SH

-Screening retrieved papers against inclusion criteria: OS, JMGR, SH, SSV

-Appraising quality of papers: OS, RSC, SSV

-Extracting data from papers: OS, JMGR, SSV

-Writing to authors of papers for additional information: OS, SSV

-Obtaining and screening data on unpublished studies: OS

Data management for the review

-Entering data into RevMan: OS, JMGR

-Analysis of data: OS, JMGR, SSV

-Interpretation of data: OS, RSC, SSV

Writing the review: OS, JMGR, RSC, SSV

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corticosteroids remains controversial. Topical corticosteroids are usually used to control inflammation using the smallest amount of the drug. Their use requires optimal timing, concomitant antibiotics and careful follow up.

Objectives—The objective of the review was to assess the clinical effectiveness and adverse effects of corticosteroids as adjunctive therapy for bacterial keratitis.

Search strategy—We searched CENTRAL, MEDLINE, EMBASE, and LILACS up to 15 January 2007. We also searched the Science Citation Index to identify additional studies that had cited the included trial, an online database of ongoing trials (www.clinicaltrials.gov), reference lists of included trials, earlier reviews and the American Academy of Ophthalmology guidelines. We also contacted experts to identify any unpublished and ongoing randomized trials.

Selection criteria—We included randomized controlled trials evaluating adjunctive therapy with topical corticosteroids in people with bacterial keratitis.

Data collection and analysis—Two review authors independently screened all the retrieved articles. Methodological quality of the one included trial was assessed using forms developed using pre-specified criteria by at least two review authors. We planned to extract data on outcomes using forms developed for the purpose. We planned to report risk ratios for dichotomous outcomes and mean differences for continuous outcomes.

Main results—A single trial was eligible for inclusion in the review. Participants in the trial were randomized using a random numbers table. Allocation concealment was not attempted. Masking of participants, and care-providers was also not attempted. Outcome assessment was conducted independently by two physicians. Neither was masked to the treatment allocation. The trial reported the healing rate of epithelial defects and improvement in visual acuity.

Authors' conclusions—There are no good quality randomized trials evaluating the effects of adjunct use of topical corticosteroids in bacterial keratitis. The only randomized trial we identified in the literature suffered from major methodological inadequacies.

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Chemotherapy; Adjuvant [methods]; Eye Infections; Bacterial [*drug therapy]; Keratitis [*drug therapy; microbiology]

MeSH check words

Humans

Background

Introduction

Keratitis or corneal inflammation is a potentially sight threatening condition which may have infectious or non-infectious etiology. Keratitis presents as a diagnostic challenge due to the large number of possibilities which may lead to this condition. Bacterial keratitis is a serious ocular infectious disease that can lead to severe visual loss. Risk factors for bacterial corneal infection include contact lens wear, ocular surface disease, corneal trauma and

previous ocular or eyelid surgery. Certain ocular diseases and systemic conditions which depress the immune system also increase the possibility of bacterial keratitis.

Topical antibiotics constitute the mainstay of treatment in cases of bacterial keratitis whereas the use of topical corticosteroids remains controversial. The role of topical corticosteroid as an adjunctive therapy for bacterial keratitis was discussed in many studies. Topical steroids are usually used to control inflammation using the smallest amount of the drug. Their use requires optimal timing, concomitant antibiotics and careful follow up. The effect of treatment on viability of bacteria in the cornea, corneal wound healing, corneal scarring, increase in intraocular pressure, clinical outcomes and adverse events should be compared between antibiotics alone and antibiotics plus corticosteroids.

Epidemiology

Approximately 30,000 cases of microbial keratitis are diagnosed annually in the United States, which includes bacterial, fungal and parasitic causes (Pepose 1992). The proportion of people who develop corneal blindness secondary to bacterial keratitis is high in developing countries (Chirambo 1986; Feng 1990). The spectrum of bacterial keratitis can also be influenced by geographic and climate factors. Many differences in keratitis profile have been noted between populations living in rural or city areas, in western or in developing countries (Baker 1996; Bennett 1998; Schaefer 2001; Vajpayee 2000).

Certain bacteria which make up the normal ocular flora are usually implicated in cases of infectious keratitis. Due to the proximity of these organisms to the cornea, they are easily inoculated into damaged or abnormal corneal tissues. Host defences are usually sufficient to prevent infection but once these are violated, for example, in trauma or debilitating diseases, florid bacterial contamination of ocular tissue may occur. Common causative organisms include staphylococci and streptococci, inherent residents of the ocular milieu (Mino 2005; Moeller 2005). In the past several years there has been an increase in the number of contact lens wearers (Poggio 1989). Incidence of bacterial keratitis secondary to use of extended-wear contact lenses is about 8,000 cases per year. Multiple organisms have been isolated from cases of microbial keratitis in association with contact lens wear (Poggio 1989). A higher prevalence of gram negative rods, such as pseudomonas, was reported in contact lens wearers compared to patients who do not use contact lenses (Dart 1991; Schein 1989).

Conditions which disrupt ocular homeostasis may set the stage for bacterial contamination of the cornea. Agricultural workers, contact lens wearers and patients who have received any form of ocular surgery or trauma all have increased risk of bacterial keratitis. Ocular surface disorders such as recurrent erosions and tear film abnormalities, lid abnormalities and use and abuse of topical medications all predispose to infections. Debilitating diseases, immunocompromised states and chronic use of immunosuppressive drugs also contribute to this disease condition (Bourcier 2003; Killingsworth 1993; Musch 1983).

Presentation and diagnosis

Patients with bacterial keratitis present with unilateral and in rare instances, bilateral, pain; and abnormal sensitivity to light, or photophobia. Corneal epithelial breaks that are

associated with ulcers expose corneal nerve endings and contribute to the pain and discomfort that is associated with this condition.

Typically, the anterior segment of the eye is inflamed and congested. Intense and diffuse conjunctival vessel injection is frequently observed. The discharge may be thick and profuse and is often mucoid to purulent in nature. The eyelids may be edematous and swollen and the underlying palpebral conjunctivae inflamed. The infected portion of the cornea will usually contain a focal area of stromal infiltrate with an overlying area of epithelial excavation. The infiltrate is often, but not always, well circumscribed with distinct borders. The cornea is edematous and the visual acuity is reduced. The severity of visual loss is dependent on the extent and location of the lesion.

Severe cases of bacterial keratitis lead to profound anterior chamber reaction and hypopyon (an accumulation of pus cells in the anterior chamber). Ciliary body inflammation sometimes causes hypotony (lower intraocular pressure); on the other hand, the presence of inflammatory cells in the aqueous may also clog the trabecular meshwork and increase the intraocular pressure.

Determining the etiology of the keratitis by taking corneal scrapes and appropriate cultures is an essential step before the use of any topical antibiotic. However, empirical therapy need not be withheld until culture results become available. Unfortunately, there are no clear-cut signs which will point to a bacterial cause of the keratitis. Patient history and on examination the status of the epithelium, the size and time to diagnosis of the corneal lesions, the degree of the stromal inflammation, the quality and quantity of discharge and other associated findings all have to be considered to arrive at a presumptive diagnosis.

The yield from microbiological investigation may be low despite direct inoculation of a sample on the culture media. However, the positive culture will guide the ophthalmologist's choice of appropriate antibiotic therapy.

Treatment options

Topical fluoroquinolone antibiotics are popular choices for initial broad spectrum therapy (Gangopadhyay 2000; Hyndiuk 1996; O'Brien 1995; OSG 1997; Parks 1993). However, resistance to these drugs may occur with some organisms (Schaefer 2001). The new generation of fluoroquinolones, such as moxifloxacin and gatifloxacin, are currently gaining in popularity and these drugs show promise in the treatment of infectious corneal ulcers (Hyon 2004; Kowalski 2003).

Dosing of the drug is often dependent on the size of the ulcer and severity of keratitis. In severe cases, subconjunctival, subtenon or intravenous antibiotics are instituted. Cycloplegic eyedrops may be given to reduce pain and inflammation.

The role of corticosteroids as adjunctive therapy for bacterial keratitis is controversial. They have consistently been avoided by practitioners for fear of causing immunosuppression and, consequently, potentiating bacterial replication. Judicious use of steroids with adequate antibiotic therapy may, however, be beneficial for the patient. Once the micro-organisms have been eliminated and adequate sterilization has been achieved, lessening the

inflammatory response through corticosteroids may reduce corneal neovascularization and scarring.

Rationale for a systematic review

Topical steroids are used to control damage from inflammation in bacterial keratitis. Although corticosteroids as an adjunctive therapy for bacterial keratitis have been discussed in many published reports, the type and concentration of corticosteroid, frequency of dosing, optimal timing with respect to the introduction of topical antibiotics and stage of healing are not consistent in the literature. A systematic review of available trials is needed to further understand the use of corticosteroids in treating bacterial keratitis and will better define their role as an adjunctive treatment modality for bacterial corneal ulcers.

Objectives

The objective of the review was to assess the effectiveness of corticosteroids as adjunctive therapy for bacterial keratitis.

Methods

Criteria for considering studies for this review

Types of studies—We included all relevant randomized controlled trials in this review.

Types of participants—We included studies in which patients were diagnosed to have bacterial keratitis either clinically or microbiologically. Studies that included participants who have mixed infections and corneal perforations that warrant surgical intervention were excluded.

Types of interventions—We included studies using corticosteroids as an adjunct to antibiotics in the management of bacterial keratitis. This included placebo-controlled trials or trials that compared different steroids against each other as adjunctive agents.

Types of outcome measures

Primary outcomes: The primary outcomes for this review were:

1. clinical improvement defined as lessening of the ocular inflammation, congestion, pain, photophobia and overall ocular discomfort; improvement in corneal clarity and visual acuity, decrease in size of infiltrate and epithelial defect;
2. clinical cure defined as complete healing of the epithelium with scarring, disappearance of any sign of inflammation such as congestion and anterior chamber cellular reaction.

Secondary outcomes: The secondary outcomes for this review were:

1. microbiologic cure defined as sterilization of the cornea and absence of bacterial viability as shown by corneal smears and cultures;
2. time to clinical or microbiologic cure.

We reported the outcomes at different times of follow up, as described in the included studies.

Adverse effects—Adverse effects of interest included:

1. persistence and progression of the corneal infection defined as increasing infiltrate size and/or bacterial colony count in smear or culture-positive isolates;
2. corneal melting, descemetocoele formation and perforation;
3. endophthalmitis;
4. increased intraocular pressure, steroid induced or inflammatory glaucoma;
5. ocular surface complications and allergic reactions attributable to the steroid application alone or to the combination of medications used;
6. recurrence of the corneal ulcer.

Other adverse effects related to topical corticosteroid therapy reported in all included studies were tabulated and included. However, it can be difficult to differentiate adverse effects of corticosteroid therapy from adverse outcomes of the progressive infections being treated.

Quality of life measures—While no data on quality of life were reported in the included trial, further updates of this review will report any data available from future trials.

Economic data—The cost of adding steroids to the therapeutic regimen in any future trials will be reported in updates of this review. No data were reported in the included trial.

Follow up: To take into account the possibility of recurrence, only studies with at least one-month follow up were included for analysis.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library*, MEDLINE, EM-BASE and Latin American and Caribbean Literature on Health Sciences (LILACS). There were no date or language restrictions. The databases were last searched on 15 January 2007.

See: Appendices for details of search strategies used for each database.

Searching other resources—We identified and screened through all studies that had cited the included trial using the Science Citation Index database. We screened through the reference lists of included studies and earlier reviews including Wilhelmus 2002 and abstracts from the American Academy of Ophthalmology meeting in 2003 (AAO 2003) to identify additional relevant studies. We contacted Dr. William Hodge for information regarding ongoing and unpublished trials. We searched the online database of ongoing clinical trials (<http://www.clinicaltrials.gov>, accessed on August 15, 2007) to identify information on ongoing trials. We did not handsearch any journals or conference proceedings specifically for this review.

Data collection and analysis

Assessment of search results—Two review authors independently reviewed the titles and abstracts resulting from the literature searches, according to the inclusion criteria stated in the protocol. The abstracts were classified as ‘definitely exclude’, ‘unsure’ or ‘definitely include’. The full text for articles in the ‘unsure’ category were obtained and re-assessed for inclusion. The author of one study labeled as ‘unsure’ was contacted for further clarification. This study is listed as awaiting assessment pending a response from the author. Disagreements were resolved through discussion. Studies labeled as ‘excluded’, by both review authors, were excluded from the review and documented along with reasons for exclusion, in the ‘Characteristics of excluded studies’ table. One trial labeled ‘included’ was further assessed for its methodological quality.

Assessment of methodological quality—Two review authors independently assessed the included study for methodological quality according to guidelines set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). Methods employed to address the following systematic biases were considered to determine the methodological quality of the included trial:

- a. Allocation concealment was assessed to be ‘adequate’, ‘inade-quate’ or ‘unclear’. Any method of allocation concealment such as centralized randomization, use of sequential opaque envelopes which provides reasonable confidence that the allocation sequence was concealed from participating physicians and patients was to be considered ‘adequate’. Trial reports without such explicit mention of a method of allocation concealment were to be assessed for convincing information on adequacy of allocation concealment. If the adequacy of allocation concealment was unclear from the trial report, we planned to contact the primary investigators for clarification. If they did not respond within a reasonable time period, we planned to classify the studies based on available information and update it as more information became available.
- b. Masking of participants, care providers and outcome assessors with regard to treatment allocation.
- c. Rates of follow up, reasons for loss to follow up and analysis by the principle of intention-to-treat. We assessed whether follow up rates for treatment and control arms were similar and whether all participants were analyzed in the group they were randomized to. We also examined whether both, participants for whom no outcome was collected, and those who received only some or none of their allotted treatment, were included in the analysis. We interpreted the analysis as an intention-to-treat only if both the above criteria were fulfilled.

Disagreements were resolved through discussion. The author of the included trial was contacted for additional information on issues that are categorized as ‘unclear’ from information available in the original report.

Data collection—Two review authors independently extracted data on outcomes listed in the ‘Criteria for inclusion of studies’ from the published report of the included trial using

data extraction forms developed for this purpose. Discrepancies were resolved through discussion. The primary investigator of the trial was contacted for information on missing or unavailable data. Two review authors independently entered the data into RevMan 4.2, using the double data entry facility.

Data synthesis—We planned to conduct data analysis according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 8 (Deeks 2006). We planned to report a summary risk ratio for dichotomous outcomes and mean difference for continuous outcomes. We planned to calculate a standardized mean difference if the outcomes were measured on different scales. Time to event data were to be reported as a summary log hazard ratio using methods described in Parmar 1998 to extract information on observed and log-rank expected events from the included studies. The inconsistency of effect estimates across studies was to be assessed using the I-squared statistic. We planned to examine the symmetry of the funnel plot. If the I-squared statistic was greater than 50%, our a priori decision was to consider it to indicate substantial heterogeneity, and not combine the study results in a meta-analysis. Instead, we planned to present a tabulated summary. In the absence of significant statistical and clinical heterogeneity, we planned to combine the results of included trials using a random-effects model. A fixed-effect model was to be used if there were fewer than three trials.

Subgroup analysis—We planned to conduct subgroup analysis based on the causative organism, if sufficient information was available from the included studies. To assess the response to treatment in bacteria with different virulence, we planned to analyze those with similar virulence together as subgroups.

Sensitivity analysis—We planned to conduct sensitivity analyses to assess how robust the review results are to key decisions and assumptions made during the review. Sensitivity analyses of data in updates of this review will be conducted with the following adjustments:

1. exclusion of studies with lower methodological quality;
2. exclusion of unpublished studies.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search—The electronic searches returned 336 articles. The titles and abstracts of these articles were screened and 16 were determined to be relevant. On review of full text articles of these papers, one trial was included in the review, one abstract is awaiting assessment and 14 abstracts were excluded from the review. The excluded studies along with reasons for exclusions are listed in the 'Characteristics of excluded studies' table. Details of the study awaiting assessment are provided in the 'Characteristics of studies awaiting assessment' table. We identified one ongoing clinical trial, Steroids for Corneal

Ulcers Trial (SCUT 2006), details of which are summarized in the 'Characteristics of ongoing studies' table.

Only one randomized controlled trial conducted in South Africa (Carmichael 1990) was eligible for inclusion in this review. Forty eyes in 39 participants were randomized. Both eyes in a person with bilateral corneal ulcers were randomized 'separately'. Details of this trial are summarized below with salient features listed in the 'Characteristics of included studies' table.

Types of participants: Participants with central or paracentral corneal ulcers were included in the trial. People under 13 years of age and people with fungal isolates, perforated ulcers, descemetocoeles, atopic ulcers, no light perception on admission, underlying viral corneal conditions were excluded from the trial. Participants presented with ulcers varied in location (central, paracentral), size, and presence of hypopyon (seen in 76% of eyes in corticosteroid group and 63% in control group). Sixty-seven per cent of eyes in the corticosteroid group and 74% in the control group were culture positive at baseline. Cultures isolated a wide spectrum of gram negative and positive bacteria. Of note was the absence of *Pseudomonas aeruginosa* isolates from any of the participants.

Types of interventions: All participants in the trial, immediately upon admission, received topical antibiotics in the form of hourly cefazolin and gentamicin eye drops, chloromycetin eye ointment at night, and subconjunctival injections of cefazolin and gentamicin on admission, the following morning and further injections as indicated by the severity of the infection. In addition, patients were administered atropine eye drops and multivitamin tablets, twice daily. Patients randomized to corticosteroid treatment were assessed after 24 hours of antibiotic therapy. If they were considered to have improved or remained the same, dexamethasone (0.1%) eye drops were administered four times a day along with the antibiotic regimen. Adjunct corticosteroid therapy was continued until healing was complete, and for a minimum of four weeks. No placebo was administered to the control group.

Types of outcomes: The trial assessed the effectiveness of the treatment in terms of rate (in mm² per day) of healing of the ulcer, and best corrected visual acuity using Snellen chart at a minimum four weeks of follow-up. Snellen visual acuity was converted to a number; no light perception was assigned the number 1 and 6/6 the number 15. The trial also reported complications in treatment and control groups.

Risk of bias in included studies

Randomization in this trial was achieved using a random numbers table. Selecting a number randomly from the page, the authors allocated eyes based on consecutive numbers in the table. Odd numbers were allocated to one treatment and even numbers to the other. Allocation was not concealed. One eye randomized to corticosteroid group did not receive treatment due to descemetocoele formation within the first 24 hours. Corticosteroid treatment was discontinued after 12 days in another eye due to development of corneal thinning and early descemetocoele formation. Neither the participants nor the physicians caring for them

were masked to the treatment allocation. Outcomes were independently assessed by two physicians, but neither was masked to the treatment allocation. The analysis was not by intention-to-treat. Six (29%) eyes in the corticosteroid group and 8 (42%) eyes in the control group were excluded from the analysis of healing rates. Reasons for exclusion included development of persistent epithelial defects (failure of ulcer to heal within 21 days), necessity for additional therapy such as pressure padding for perforations or corneal thinning, and uncontrolled infection. Analysis for visual acuity outcomes included only those eyes that healed.

Effects of interventions

No data were available from the included trial on outcomes specified in the protocol for this review. The original data for the study could not be located by the primary investigator. We have discussed appropriate outcomes for trials assessing the effectiveness of adjunct corticosteroid treatment for bacterial corneal ulcers in the 'Implications for research' section of this review. Here, we have summarized the outcomes reported in Carmichael 1990.

The trial reported a healing rate of 0.36 mm² per day in the corticosteroid group and 0.30 mm² per day in the control group. The difference was not statistically significant. Though improvement in visual acuity from baseline was statistically significant in both groups, there was no significant difference between the two treatment groups.

One eye in each group experienced perforation, corneal thinning and epithelial breakdown (breakdown of epithelium after initial healing). Two eyes in the control group had uncontrolled infection. Recurrence of infection (recurrence of hypopyon within one week of discharge after adequate treatment of infection) occurred in one eye in the corticosteroid group and two eyes in the control group. Persistent epithelial defect was reported in four eyes in the corticosteroid group and three eyes in the control group. Though the overall number of complications was more in the control group (10) compared to that in corticosteroid group (8), the small number of participants in each group and the significant proportion of exclusions from analysis preclude drawing definite conclusions on complications as well as those on healing rates and visual acuity improvement. For details of complications reported in the included trial, see Table 1.

Discussion

Microbial keratitis is a potentially sight threatening condition, and an important cause of corneal inflammation. It has been estimated that 500,000 persons develop ulcerative keratitis annually around the world (Wilhelmus 2002).

As the mainstay of treatment for bacterial keratitis, topical antibiotics are used primarily to eliminate the causative organisms. However, host corneal inflammatory response may in some cases cause more damage than the infection itself. The use of topical corticosteroids in addition to antimicrobial therapy in the treatment of bacterial keratitis has been controversial for over 50 years. Their anti-inflammatory activity may help control the host response, reduce corneal neovascularization and scarring, thus favouring the clinical outcome. On the

other hand, the immunosuppressive effect of corticosteroids may actually promote bacterial replication and slow recovery of the patient.

The effectiveness and safety of topical corticosteroid use adjunctive to antibacterial therapy in bacterial keratitis has yet to be determined. The reports of this treatment modality have, thus far, been inconsistent. The paucity of controlled clinical trials makes it impossible to develop standardized treatment recommendations.

In this review, only one randomized clinical trial was identified (Carmichael 1990). Assessment of quality as per pre-specified criteria determined that the trial methodology was inadequate. Allocation concealment, which has been shown empirically to significantly influence methodological quality in randomized trials (Schulz 2002), was not attempted in this trial. No data was available from the included trial on outcomes specified in the protocol for this review. Based on an analysis which was not by intention-to-treat, the authors of this trial reported no statistically significant difference in final visual acuity, healing rate, or incidence of complications when comparing the topical antibiotic only (n=21) versus the antibiotic + topical corticosteroid groups (n=19). However, the trial design was not substantiated by a priori sample size calculation and the lack of evidence of difference might as well have been due to a high type II error. No adverse effects were encountered when using dexamethasone 0.1% four times a day in addition to topical antimicrobial therapy. The authors suggested that steroid treatment should be initiated 24 hours after antimicrobial therapy. Other helpful suggestions for clinicians have been proposed by Wilhelmus 2002.

Authors' Conclusions

Implications for practice

The effectiveness of corticosteroid as an adjunctive treatment for bacterial keratitis is uncertain at present. The single randomized clinical trial included in this review is inconclusive. Interestingly there were no uncontrolled infections found in the corticosteroid treated group.

Although many currently recommend waiting at least 24 hours before instituting corticosteroid therapy, there is actually no evidence available that argues against immediate institution concurrent with antibiotic therapy. Identification of the bacterial pathogen is crucial for appropriate selection of antibiotics. Close observation for complications and wound healing is essential. It is prudent to reduce or discontinue corticosteroid treatment if healing is delayed. But these recommendations are not supported by any evidence in this review.

Implications for research

There is a clear need for adequately designed and well conducted randomized controlled clinical trials to evaluate the effectiveness of topical corticosteroids as adjunctive therapy in management of bacterial corneal ulcers. In severe bacterial keratitis where corneal scarring is of great concern, there is hope that adjunctive topical corticosteroid might be of some benefit with respect to treatment outcome. However, to demonstrate this benefit a classification of disease severity and larger studies are needed. With modern clinical

imaging techniques, the assessment of ulcer severity as well as treatment results should be more reliable.

Gritz 2007 reported a sample size requirement of 165 to detect a 30% difference in change in visual acuity with a power of 80%. However, based on the Hyndiuk 1996 study evaluating the outcomes selected for this systematic review, assuming that 74% of participants would successfully improve clinically, one would require a sample size of 74 participants in each group in a two-arm randomized trial to detect a difference in proportion of participants with clinical improvement of 20% with 90% power. Adequate attention should be paid to the method of randomization, stratification by organism causing keratitis (Gram positive/Gram negative), depth of the corneal ulcer, and allocation concealment in the design and conduct of future randomized trials for this question.

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Characteristics of Studies

Characteristics of included studies *[ordered by study ID]*

Carmichael 1990

Methods	<p>Method of randomization: Randomization was done using a random numbers table. The first case number was randomly selected, with odd numbers being allocated to one treatment group and even numbers to the other.</p> <p>Number randomized: 40 eyes of 39 participants; 21 eyes to steroid group, 19 eyes to non-steroid group</p> <p>Exclusions after randomization and reasons for exclusion: 1 patient (1 eye) in the steroid group did not receive treatment due to descemetocoele formation the morning after admission. Another patient (1 eye) had corneal thinning with early descemetocoele formation and steroids were discontinued after 12 days.</p> <p>Losses to follow-up and reasons for loss to follow-up: None reported</p> <p>Number analyzed: Healing rates were calculated with data available only for 15 eyes in steroid group and 11 eyes in non-steroid group. Patients were excluded from analysis if they had persistent epithelial defects (more than 21 days), required therapy other than that in the protocol such as pressure padding for perforations or corneal thinning and if they had uncontrolled infection that did not heal</p> <p>Analysis of visual acuity at 2 months included only 15 eyes in steroid group and 13 eyes in non-steroid group</p> <p>Intention to treat analysis (ITT): Not an ITT</p> <p>Masking of participants: Not done</p> <p>Masking of care-givers: Not done</p>
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	Masking of outcome assessment: All assessments were independently conducted by two unmasked physicians
Participants	<p>Country: South Africa</p> <p>Study period: Not reported</p> <p>Age: Ranged from 19 to 81 years. Mean age was 51.6 years in steroid group and 51.4 years in non-steroid group</p> <p>Gender: 10% of participants in steroid group and 24% in non-steroid group were female</p> <p>Inclusion criteria: Central or paracentral corneal ulcers severe enough to warrant admission in the hospital</p> <p>Exclusion criteria: Identification of fungal isolates, perforated ulcers or descemetocoeles, underlying viral corneal conditions, atopic ulcers, no light perception on admission, less than 13 years of age</p> <p>Equivalence of baseline characteristics: There were fewer females in the steroid group Greater number of eyes in steroid group had paracentral ulcers (14) compared to non-steroid group (10) Greater number of eyes in steroid group (16) had hypopyon at admission compared to non-steroid group (12)</p>
Interventions	<p>Treatment or Intervention 1: 0.1% dexamethasone eye drops four times a day were added to the above treatment on the day following admission if the condition of the ulcer was adjudged to be the same or improved</p> <p>Control or Intervention 2: No additional corticosteroid therapy</p> <p>Treatment for all participants in the two groups included: 32 g/l cefazolin eye drops and 14 g/l gentamicin eye drops hourly, 1% atropine eye drops twice a day, chloromycetin eye ointment at night and twice daily multi-vitamin tablets; Sub-conjunctival injection of 125mg cefazolin and 20mg gentamicin into a bleb of lignocaine were given on admission, the morning following admission and one or two additional injections as indicated by the severity of the infection</p>
Outcomes	<p>Primary outcome: Healing rate of ulcer; each ulcer was drawn to scale on to a 1 mm ruled graph paper and number of squares was counted to calculate the area for each ulcer at admission and to calculate the area of ulcer healed per day</p> <p>Secondary outcomes: Visual acuity, measured with Snellen charts by two physicians independently. Visual acuity was categorized using an arbitrary scale to compare the improvement in the two treatment arms</p>
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Barequet 2001	Not randomized
Buhren 2001	Non-comparative case report
Callegan 1994	Review article, no new randomized trial described
Cosar 2004	Not randomized
Goldberg 2002	Case report
Gris 2004	Case report
Hanada 2001	Not randomized, no clear mention of inclusion of bacterial keratitis
Hoffman 2003	Cohort study
Morlet 1999	Cross-sectional study
Nakajima 2001	Retrospective study
Shulman 1996	Inclusion criteria do not include bacterial keratitis
Vajpayee 1998	Retrospective study

Wilhelmus 2002 | Review article, no new randomized trial described

Characteristics of ongoing studies [ordered by study ID]

SCUT 2006

Trial name or title	Steroids for Corneal Ulcers Trial (SCUT)
Methods	
Participants	<ol style="list-style-type: none"> 1 Corneal ulcer with epithelial defect greater than 1 mm at its greatest depth 2 Positive bacterial culture <p>Exclusion criteria: Evidence of fungus on KOH or gram stain or culture; acanthamoeba infection; herpes keratitis; previous history of corneal ulcer; vision less than 6/60 in fellow eye</p>
Interventions	<p>Treatment: moxifloxacin 0.5% + PSP 1%</p> <p>Control: moxifloxacin 0.5% + placebo (0.9% NaCl solution)</p>
Outcomes	<p>Primary outcome: Best spectacle-corrected logMAR visual acuity three months after enrollment, using best spectacle-corrected enrollment visual acuity as co-variate</p> <p>Secondary outcomes:</p> <ol style="list-style-type: none"> 1 Infiltrate size at 3 months after enrollment 2 Best hard contact lens visual acuity at 3 months after enrollment 3 Time to resolution of epithelial defect after enrollment 4 Ocular perforations 5 Best spectacle-corrected logMAR visual acuity 12 months after enrollment
Starting date	September 2006
Contact information	<p>United States: Proctor Foundation, UCSF, San Francisco, California, 94143</p> <p>Recruiting:</p> <p>Stephanie Costanza, M.A. 415-476-2463 stephanie.costanza@ucsf.edu</p> <p>Jenafir House, MPH, MSW 415-514-1616 jenafir.house@ucsf.edu</p> <p>Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, 03756</p> <p>Recruiting: Christine Toutain, PhD 603-653-3178 Christine.M.Toutain@Dartmouth.EDU</p> <p>India:</p> <p>Aravind Eye Hospital, Madurai, Tamil Nadu, 625 020, India; Recruiting</p> <p>S Chandravathi +91 (452) 535-6100 childreneye@aravind.org</p> <p>RMahalakshmi +91 (452) 535-6100 eyebank@aravind.org</p> <p>S Chandravathi +91 (452) 535-6100 childreneye@aravind.org</p> <p>M Meena lasik@tv1.aravind.org</p> <p>R Revathi, MD +91 (422) 436-0400 revathi@cbe.aravind.org</p>
Notes	<p>United States: Proctor Foundation, UCSF, San Francisco, California, 94143</p> <p>Recruiting:</p> <p>Stephanie Costanza, M.A. 415-476-2463 stephanie.costanza@ucsf.edu</p> <p>Jenafir House, MPH, MSW 415-514-1616 jenafir.house@ucsf.edu</p> <p>Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, 03756</p> <p>Recruiting: Christine Toutain, PhD 603-653-3178 Christine.M.Toutain@Dartmouth.EDU</p> <p>India:</p> <p>Aravind Eye Hospital, Madurai, Tamil Nadu, 625 020, India; Recruiting</p> <p>S Chandravathi +91 (452) 535-6100 childreneye@aravind.org</p> <p>R Mahalakshmi +91 (452) 535-6100 eyebank@aravind.org</p> <p>S Chandravathi +91 (452) 535-6100 childreneye@aravind.org</p> <p>M Meena lasik@tv1.aravind.org</p> <p>R Revathi, MD +91 (422) 436-0400 revathi@cbe.aravind.org</p>

Data and Analyses

This review has no analyses.

Appendix 1. CENTRAL search strategy used for Issue 4, 2006

- #1 MeSH descriptor Keratitis
- #2 MeSH descriptor Corneal Ulcer
- #3 MeSH descriptor Eye Infections, Bacterial
- #4 cornea* near ulcer*
- #5 keratitis near bacteria*
- #6 bacteri* near infec* near ocular
- #7 bacteria* near infec* near eye*
- #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
- #9 MeSH descriptor Adrenal Cortex Hormones
- #10 steroid*
- #11 corticosteroid*
- #12 (#9 OR #10 OR #11)
- #13 (#8 AND #12)

Appendix 2. MEDLINE search strategy on OVID used up to January 2007

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp keratitis/
14. exp corneal ulcer/
15. exp eye infections bacterial/
16. (cornea\$ adj3 ulcer\$).tw.

17. (keratitis adj3 bacteria\$.tw.
18. (bacteri\$ adj3 infec\$ adj5 ocular).tw
19. (bacteri\$ adj3 infec\$ adj5 eye\$.tw.
20. or/13-19
21. exp adrenal cortex hormones/
22. steroid\$.tw.
23. corticosteroid\$.tw.
24. or/21-23
25. 20 and 24
26. 12 and 25

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE search strategy for Ovid used up to January 2007

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$.tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/

19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp keratitis/
34. exp cornea ulcer/
35. exp eye infection/
36. (cornea\$ adj3 ulcer\$).tw.
37. (keratitis adj3 bacteria\$).tw.
38. (bacteri\$ adj3 infec\$ adj5 ocular).tw.
39. (bacteri\$ adj3 infec\$ adj5 eye\$).tw.
40. or/33-39
41. exp corticosteroid therapy/
42. steroid\$.tw.
43. corticosteroid\$.tw.
44. or/41-43
45. 40 and 44
46. 32 and 45

Appendix 4. LILACS search terms used on 15 August 2007

kerat\$ and bacteria\$ and steroid\$

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Plain Language Summary

Topical corticosteroids as adjunctive therapy for bacterial keratitis

Bacterial keratitis or corneal inflammation due to bacterial infection, is a potentially sight threatening condition. Risk factors for bacterial keratitis, a serious ocular condition that can result in visual disability, include contact lens wear, ocular surface disease, corneal trauma and previous ocular or eyelid surgery. Topical antibiotics are the mainstay of treatment for bacterial keratitis. The usefulness of adjunct treatment with topical corticosteroids is controversial. We identified a single randomized trial of borderline methodological quality, evaluating adjunct corticosteroid therapy for bacterial keratitis. We do not have sufficient evidence to determine the effects of adjunct treatment with topical corticosteroids for bacterial keratitis.

Table 1
Complications reported in included studies

Complication	Corticosteroids (21)	Antibiotics (19)
Corneal perforation	1	1
Corneal thinning	1	1
Uncontrolled thinning	0	1
Recurrence of infection	1	2
Persistent epithelial defect	4	3
Epithelial breakdown	1	1