Evidence-based treatment of herpes simplex virus keratitis: a systematic review

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CRD summary
This review concluded that trifluridine, acyclovir and possibly interferon were effective for herpes simplex virus epithelial keratitis. Corticosteroids with an antiviral were effective for Herpes simplex virus stromal keratitis and long-term acyclovir reduced recurrence. The validity of these conclusions may be limited by the small size of studies, restriction to articles published in English and the method of data extraction.

Authors' objectives
To systematically review randomised controlled trials for Herpes simplex virus epithelial and stromal keratitis in order to establish an evidence-based foundation for treatment.

Searching
MEDLINE was searched from January 1966 to May 2006 for studies published in English. Search terms were reported. Reference lists of identified articles were searched.

Study selection
To be eligible for inclusion, studies had to be prospective, randomised, double-blinded, controlled, compare any treatment for Herpes simplex virus keratitis with any other treatment or placebo, use specific clinical criteria for diagnosis and outcomes and include a description of the statistical analysis used. The reported outcomes were healing defined by fluorescein or rose bengal staining, slit lamp evaluation and in one study, polymerase chain reaction for Herpes simplex virus DNA and viral culture.

In the trials of Herpes simplex virus epithelial keratitis, 16 used acyclovir ophthalmic ointment (3%) or 400mg orally, seven used trifluridine (1% to 2%) in various preparations, adenine arabinoside (five trials, 1% to 3%), bromovinyl deoxyuridine (two trials, 0.1% to 1%), epidermal growth factor (one trial, 10µg/mL), human leukocyte interferon (six trials, 107 IU/mL), idoxuridine (three trials, 0.5% to 5%), vidarabine (six trials, 3%), foscarinet (one trial, 3%), thermocautery (one trial), minimal wiping debridement (one trial) and placebo alone or in combination (11 trials).

In the trials of Herpes simplex virus stromal keratitis, acyclovir was used in six trials (3% or 400mg orally), betamethasone (two trials, 0.01% to 0.1%), trifluridine (three trials, 1%), prednisone (two trials, 1%), dexamethasone (one trial, 0.01%), flurbiprofen (one trial, 0.03%). Placebo was used in all trials, alone or in combination.

Three reviewers independently determined the eligibility of each article for inclusion. Only studies uniformly agreed upon as meeting the criteria were included.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Data were synthesised narratively. Whether or not a significant difference was reported was extracted from each study.

Results of the review
Thirty-seven studies met the inclusion criteria: 30 for Herpes simplex virus epithelial keratitis (1,786 participants) and seven for stromal keratitis (1,315 participants). The number of participants in each study ranged from 10 to 287.

There was no significant difference between groups in 20 of the 30 trials of Herpes simplex virus epithelial keratitis.
Acyclovir was superior to placebo, adenine arabinoside and idoxuridine (one study each). In one study, acyclovir in combination with minimal wiping debridement was superior to minimal wiping debridement alone. Trifluridine was superior to adenine arabinoside and idoxuridine (one trial each). Addition of human leukocyte interferon to acyclovir (two trials) and trifluridine and bromovinyl deoxyuridine (one study each) was superior to these agents alone.

There was no significant difference in two of the seven trials in Herpes simplex virus stromal keratitis. Betamethasone (two trials), dexamethasone (one trial), flurbiprofen (one trial) in combination with acyclovir were superior to acyclovir alone. Acyclovir (one trial) and prednisone (one trial) were also superior to placebo.

Authors’ conclusions
The best evidence for the treatment of Herpes simplex virus epithelial keratitis supported the use of topical trifluridine and topical or oral acyclovir and suggested an additional benefit from topical interferon. The best evidence for the treatment of Herpes simplex virus stromal keratitis supported the use of topical corticosteroids given with a prophylactic antiviral. Long-term suppressive oral acyclovir therapy appeared to reduce the incidence of recurrent Herpes simplex virus keratitis.

CRD commentary
The inclusion criteria appeared adequate. However, the search of only one database may have missed relevant studies and the restriction to studies published in English could have introduced language bias. Appropriate methods were used to minimise errors and bias in study selection, but it was unclear whether similar methods were used for data extraction. Validity was not formally assessed and limited details of included studies were reported, which made it difficult to assess the quality of the evidence on which the review findings were based. A narrative synthesis was appropriate, but the synthesis provided was of limited usefulness as conclusions were based on individual studies, most of which had a small number of participants. These limitations made the reliability of the authors' conclusions uncertain.

Implications of the review for practice and research
Practice: The authors stated that the evidence supported use of topical trifluridine and topical or oral acyclovir for Herpes simplex virus epithelial keratitis and suggested an additional benefit from topical interferon. The evidence for the treatment of Herpes simplex virus stromal keratitis supported topical corticosteroids given together with a prophylactic antiviral and long-term suppressive oral acyclovir therapy to reduce the incidence of recurrent Herpes simplex virus keratitis.

Research: The authors did not state any implications for further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.