Primary care management of acute herpes zoster: systematic review of evidence from randomized controlled trials

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Authors' objectives
To determine the efficacy of available therapies in the treatment for herpes zoster, in reducing the incidence of postherpetic neuralgia.

Searching
MEDLINE on DATASTAR and CD-PLUS, was searched from 1966 to 1993 using the search term 'herpes zoster' in combination with 'randomized controlled trials' or 'prospective', 'random allocation' or 'double-blind method'. Randomised trial citations, previous reviews, major medical textbooks and texts on infectious diseases were handsearched. The authors' own database of randomised trials in primary care literature, published and unpublished clinical trials from appropriate pharmaceutical companies, relevant abstracts and conference proceedings were also examined.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were included.

Specific interventions included in the review
Antiviral agents, corticosteroids and other compounds (levodopa and cimetidine) for the treatment of herpes zoster to reduce the incidence of postherpetic neuralgia

Participants included in the review
The age and source of study populations are given: participants were aged from 11 to 92 years, and were taken from both community and hospital settings, including both medical and eye centres.

Outcomes assessed in the review
Prevalence of pain at 1, 3 and 6 months from onset of pain.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Studies on the treatment of acute herpes zoster which had: (1) at least 2 treatment groups; (2) treatment allocated by formal randomisation; (3) data available on prevalence of pain at a minimum of 1 month; and (4) treatment feasible for routine use by general practitioners. Two investigators assigned a 3-point quality score measuring control of selection bias at entry, after entry and in assessment of outcome. Inter-rater reliability was assessed, and any disagreements were resolved by discussion.

Data extraction
The data were extracted by two investigators onto coded forms, and any disagreements were resolved by discussion. If necessary, the authors of the primary studies were approached for clarification.

Methods of synthesis
How were the studies combined?
If no heterogeneity was found between studies, fixed-effect meta-analysis was used to combine studies. If the studies were found to be heterogeneous, no combination was undertaken.

How were differences between studies investigated?
The overall quality of all studies for each type of intervention was reported as the percentage of the maximum score achievable. A qualitative description of differences between studies was given for each intervention.

Results of the review
Twenty-one studies in total: 8 studies evaluating acyclovir versus placebo; 1 study for each of idoxuridine versus acyclovir, levodopa versus placebo and cimetidine versus placebo; 6 studies of other antivirals versus placebo; and 4 studies of corticosteroids versus placebo.

Acyclovir: trials of oral acyclovir had relatively high quality scores and could be combined as no heterogeneity was detected. The pooled estimate effect found a statistically-significant reduction in pain at 3 months (odds ratio, OR, of benefit 0.65, 95% confidence interval, CI: 0.46, 0.93), but no statistically-significant benefit at either 1 or 6 months. In 2 studies, which did report a benefit, analgesic consumption was not significantly different between treatment and control groups. In addition, one of these studies had a lower quality rating than others in the group due to large drop-out. Minor adverse effects were reported in all studies, with similar incidence in both treatment and control groups.

Idoxuridine: 2 of the 3 studies found beneficial effects on pain reduction at 1 month, but not at 6 months. The studies were too heterogeneous to be combined and the overall quality scores for these studies were lower than the acyclovir studies.

Other antivirals: one small study of adenosine monophosphate versus placebo showed a benefit, but there were significant baseline differences in the characteristics of the study group. Two small studies with limited follow-up showed beneficial results for both amantadine and levodopa versus placebo. One study of cimetidine and one study of isoprinosine failed to find any treatment benefit versus placebo.

Corticosteroids: overall, the quality scores for the 4 studies were lower than the acyclovir studies. The studies exhibited significant heterogeneity at both 6 weeks and 6 months, and were not combined. Two studies were combined for effect at 3 months and a combined effect was found (OR 0.16, 95% CI: 0.06, 0.42). The study to show the strongest effect was methodologically weakest (no blinding), whilst the study that was methodologically strongest showed no effect at 6 months (shorter-term results were not reported). The adverse effect of the theoretical risk of promoting dissemination of localised zoster was not observed in the studies.

Cost information
The cost of acyclovir is £113 for 800 mg of Zovirax (Wellcome) given 5 times daily over a 7-day period (35 tablets). The typical cost of idoxuridine is £39.

Authors' conclusions
The data from clinical trials do not provide clear evidence for the efficacy of drugs, currently marketed for acute herpes zoster, in preventing postherpetic neuralgia. Variations in the definition and reporting of postherpetic neuralgia create difficulties in combining data from different studies. The inconclusive nature of the available research is disappointing, and is largely related to sample size. Conducting large trials in multiple primary care settings is a daunting prospect, but proceeding with small studies that have little chance of providing useful answers represents a poor investment of resources. Pending further research, individual clinicians trying to decide how to treat herpes zoster will have to exercise their judgement, weighing-up other factors such as toxicity and cost in their decision.

CRD commentary
A well-structured and thorough review, with clear explanation of both methodology and results. The restriction of participants to immunocompetent adults is stated in the summary, but not in the main text. The majority of included
studies involved adults over 18; others involved participants aged from 11 to 89 years (1 study), over 16 (2 studies) and
16 to 81 years (1 study). It would have been useful to have had more explanation of the heterogeneity found between
studies.

Implications of the review for practice and research
There is a need for further large clinical trials.

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