Corticosteroids for preventing postherpetic neuralgia (Review)

Chen N, Yang M, He L, Zhang D, Zhou M, Zhu C

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[Intervention Review]

Corticosteroids for preventing postherpetic neuralgia

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ABSTRACT

Background

Postherpetic neuralgia is a common serious complication of herpes zoster. Corticosteroids are anti-inflammatory and might be beneficial.

Objectives

To examine the efficacy of corticosteroids in preventing postherpetic neuralgia.

Search strategy

We updated the searches for randomised controlled trials of corticosteroids for preventing postherpetic neuralgia in MEDLINE (January 1950 to February 2010), EMBASE (January 1980 to February 2010), LILACS (January 1982 to February 2010), the Chinese Biomedical Retrieval System (1978 to 2010) and the Cochrane Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2010). We also reviewed the bibliographies of identified trials, contacted authors and approached pharmaceutical companies to identify additional published or unpublished data.

Selection criteria

We included all randomised controlled trials involving corticosteroids given by oral, intramuscular or intravenous routes for people of all ages with herpes zoster of all degrees of severity within seven days after onset, compared with no treatment or placebo, but not with other treatments.

Data collection and analysis

Two authors identified potential articles, extracted data and assessed quality of each trial independently. Disagreement was resolved by discussion with other co-authors.

Main results

Five trials were included with 787 participants in total. All were randomised, double-blind, placebo-controlled parallel group studies. No new trials were identified in the 2010 update. In the updated version we conducted a meta-analysis of two trials, and the results showed that oral corticosteroids did not prevent postherpetic neuralgia six months after the herpes onset (RR, 0.95; 95% CI 0.45 to 1.99). The three other included trials also had similar results although their data could not be included in the meta-analysis. Adverse events during or within two weeks after stopping treatment were reported in all five included trials. There were no significant differences in serious or non-serious adverse events between the corticosteroids and placebo groups.

Authors' conclusions

Corticosteroids given acutely during zoster infection are ineffective in preventing postherpetic neuralgia. In people with acute herpes zoster the risks of administration do not appear to be great. Corticosteroids have been recommended to relieve the zoster-associated pain in the acute phase of disease; if further research is designed to evaluate the efficacy of corticosteroids for herpes zoster, long-term follow-up should be included to observe their effect on the transition from acute pain to postherpetic neuralgia. Future trials should include measurements of function and quality of life.

PLAIN LANGUAGE SUMMARY

Corticosteroids for preventing postherpetic neuralgia

Postherpetic neuralgia is a painful condition that is one of the most common complications of an acute herpes zoster infection. It presents as a localised rash resembling chicken pox, often called 'shingles'. Postherpetic neuralgia may persist until death and has major implications for quality of life and use of healthcare resources. Corticosteroids have a potent anti-inflammatory action which might minimise nerve damage and thereby relieve or prevent the pain of people suffering from this condition. Five trials were included in the review. There was no significant difference between the corticosteroid and control groups in the presence of postherpetic neuralgia six months after the onset of acute herpetic rash. There was also no significant difference between the treatment groups and placebo groups in the secondary outcome analyses and subgroup analyses. It can be concluded that corticosteroids are ineffective in preventing postherpetic neuralgia. No significant adverse events were noted in patients with shingles taking prednisolone. Corticosteroids used for other indications during acute zoster infection appear to be as safe as when no infection is present.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Corticosteroids for acute herpes zoster to prevent postherpetic neuralgia

Patient or population: patients with acute herpes zoster to prevent postherpetic neuralgia
Settings: hospitals and clinics
Intervention: Corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Corticosteroids				
Presence of PHN six months after the onset of the acute herpetic rash clinical manifestation Follow-up: 6-23 months	**193 per 1000**	**183 per 1000** (87 to 384)	**RR 0.95** (0.45 to 1.99)	114 (2 studies)	⊕⊕⊕○ **moderate**[1]	
Serious adverse events clinical manifestation and laboratory examination Follow-up: 6-23 months	**8 per 1000**	**13 per 1000** (3 to 42)	**RR 1.65** (0.38 to 5.29)	755 (5 studies)	⊕⊕⊕○ **moderate**[1]	
Non-serious adverse events clinical manifestation and laboratory examination Follow-up: 6-23 months	**113 per 1000**	**147 per 1000** (102 to 211)	**RR 1.30** (0.9 to 1.87)	755 (5 studies)	⊕⊕⊕○ **moderate**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] There is a high risk of bias due to inadequately addressed incomplete outcome data of the Esmann 1987 trial, in which six patients were withdrawn, but the reasons and assigned groups of five cases were not specified.

BACKGROUND

Postherpetic neuralgia (PHN) is a painful condition that occurs in people following an acute herpes zoster infection (commonly referred to as 'shingles'). Shingles is an acute vesicular eruption involving one or two adjacent dermatomes, with pain often preceding the eruption by days to weeks (Kost 1996). Herpes zoster results from reactivation of the varicella-zoster virus acquired during chicken pox, the primary varicella infection. Reactivation of latent varicella-zoster virus from dorsal root ganglia is responsible for the classic dermatomal rash and pain that occurs with herpes zoster (Kost 1996).

Herpes zoster is a sporadic disease with an estimated lifetime incidence of 10 to 20%. Its incidence increases sharply with advancing age, roughly doubling in each decade past the age of 50 years. Herpes zoster is uncommon in people less than 15 years old. The normal age-related decrease in cell-mediated immunity is thought to account for the increased incidence in older age (Stankus 2000). People with disease states that affect cell-mediated immunity, such as human immunodeficiency virus (HIV) infection and certain malignancies, are at increased risk. Chronic corticosteroid use, chemotherapy and radiation therapy may increase the risk of developing herpes zoster (Fillet 2002). Ethnic background may influence susceptibility to herpes zoster. Black people are one fourth less likely than white people to develop it. Although herpes zoster is not as contagious as primary varicella infection, people with reactivated infection can transmit varicella-zoster virus to non-immune contacts. There is no seasonal incidence and the areas affected tend to be on the chest and abdomen and the territory of the ophthalmic division of the trigeminal nerve.

PHN is one of the most common complications of herpes zoster. It may persist until death and has major implications for quality of life and use of healthcare resources. Although PHN has been defined in different ways, recent data support the distinction between acute (within 30 days of rash onset), subacute (30 to 120 days after rash onset), and postherpetic neuralgia (defined as pain lasting at least 120 days from rash onset) (Desmond 2002; Dworkin 1994).

Although age, acute pain severity and rash severity appear to be correlated with incidence of PHN, accurate predictors for PHN have not been defined (Johnson 2003). About 20% of people with herpes zoster develop PHN. Its incidence is between 9 and 14% one month after the herpes zoster eruption. The most established risk factor is age. As age increases, the risk and duration of PHN also rises (Griffin 1998; Rosler 1996). The incidence of PHN after an outbreak of shingles is 10% in people over 40 years, and 20 to 50% in people over 60 years. PHN is rarely seen in people under 30 years. Other possible risk factors for the development of PHN are ophthalmic zoster, prodromal pain before the appearance of skin lesions and an immunocompromised state (Stankus 2000).

There is a tendency for PHN to improve with time and as few as 3% of people are left with severe PHN after one year. However some series report that as many as 40% of people with PHN will continue to have long-term problems because of incomplete or no pain relief from treatments. There is no way of predicting who will recover (de Moragas 1957).

Varicella-zoster virus is a highly contagious DNA virus. It is thought that the varicella virus passes to the dorsal root ganglion via the skin during the initial infection (chicken pox) and lies dormant. The latent virus becomes reactivated when immune mechanisms are impaired and is manifested by the rash and the pain. The pathophysiology of PHN remains unclear. However, pathologic studies have demonstrated damage to the sensory nerves, sensory dorsal root ganglia and dorsal horns of the spinal cord. The presence of PHN may reflect the persistence of more than the low amounts of varicella-zoster virus found during latency with continued inflammation. If this is the case, there may be a rationale for the aggressive treatment of people who have zoster with acyclovir and perhaps corticosteroids (Mahalingam 1993; Smith 1978).

The treatment of herpes zoster has three major objectives: (1) treatment of the acute viral infection, (2) treatment of the acute pain associated with herpes zoster and (3) prevention of PHN. Antiviral agents, oral corticosteroids and adjunctive individualised pain-management modalities are used to achieve these objectives.

Treatment of PHN is difficult, and a variety of treatments are offered without consensus about their effectiveness. The complexity of the underlying changes might account for the lack of efficacy of a single therapeutic approach (Alper 2002; Dworkin 2000; Johnson 2003). The effectiveness of antiviral agents in preventing PHN has been evaluated in a separate Cochrane review; it concluded that oral acyclovir was ineffective in reducing the incidence of PHN, while insufficient evidence was found to recommend other antiviral treatments to prevent PHN (Li 2009).

Some older studies designed to evaluate the effectiveness of corticosteroids such as prednisolone or triamcinolone prednisone therapy in preventing PHN have suggested decreased pain at three and 12 months (Eaglstein 1970; Keczkes 1980). Other studies have demonstrated no significant benefit (Lancaster 1995; Volmink 1996). Another two large, randomised, placebo-controlled trials evaluated the combination of corticosteroids and the antiviral agent acyclovir. One claimed that the addition of prednisone reduced the incidence and severity of acute pain but provided no additional benefit for long-term pain over acyclovir alone (Wood 1994b). The other suggested that acyclovir and a corticosteroid did not alter the course of long-term zoster associated pain significantly, but might improve quality of life (Whitley 1996). Despite the lack of clear evidence, corticosteroids are commonly used in the treatment of herpes zoster. So a systematic review of corticosteroids for preventing PHN is needed.

The first version of this Cochrane review published in 2008 indicated that there was insufficient evidence to draw any conclusion about the efficacy of corticosteroids in preventing PHN. This update did not find any new studies to alter this conclusion.

OBJECTIVES

The objective of this review was to examine the efficacy of corticosteroids in preventing PHN.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomised controlled trials (RCTs) for corticosteroids for preventing PHN after an acute herpes zoster infection irrespective of any language restrictions.

Types of participants

We included people of all ages with herpes zoster of all degrees of severity within seven days after the onset.

Types of interventions

We included all kinds of corticosteroids including hydrocortisone, prednisone, prednisolone, triamcinolone and dexamethasone given by oral, intramuscular or intravenous routes during the acute stage (starting within one week of the onset of the rash). We included trials which compared corticosteroids with no treatment or placebo, but not with other treatments. It is intended that another review will include comparisons of corticosteroids with antiviral agents. We also included trials which compared corticosteroids plus routine treatment with placebo plus routine treatment. Other forms of administration of corticosteroids such as epidural injection or topical administration were not included.

Types of outcome measures

Primary outcomes

The primary outcome measure was the presence of PHN six months after the onset of the acute herpetic rash. PHN was defined according to clinical diagnostic criteria as pain persisting, or recurring, at the site of shingles at least one month after the onset of the acute rash (MacDonald 2000).

Secondary outcomes

Secondary outcome measures were:

1. Pain severity measured by a validated visual analogue scale or numerical descriptive scale after three, six and 12 months.
2. Quality of life measured with the short form 36 questionnaire (SF-36) (Ware 1998) after six months.
3. Adverse events during or within two weeks after stopping treatment. Adverse events were categorised as serious or not serious. Serious adverse events were those which were life-threatening, required or prolonged hospitalisation, or caused death.

Search methods for identification of studies

We searched for all randomised controlled trials for corticosteroids for preventing PHN after an acute herpes zoster infection irrespective of any language restrictions.

We searched the Cochrane Neuromuscular Disease Group Trials Register for randomised trials or quasi-randomised controlled trials. The following search terms were used singly and/or in appropriate combinations: 'herpes zoster', 'shingles', 'postherpetic' or 'post-herpetic', 'neuralgia' or 'neuropathy' or 'pain', 'glucocorticoids', 'adrenal cortex hormones', 'corticosteroid', 'steroid', 'prednisolone', 'triamcinolone', 'dexamethasone', 'hydrocortisone' and 'prednisone'. We adapted this strategy to search MEDLINE (January 1950 to February 2010), EMBASE (January 1980 to February 2010) and LILACS (January 1982 to February 2010), and the Cochrane Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2010) and the Chinese Biomedical Retrieval System (January 1978 to February 2010). We also reviewed the bibliographies of the randomised and quasi-randomised trials identified, contacted the authors and known experts in the field and approached pharmaceutical companies to identify additional published or unpublished data.

See Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5 for MEDLINE, EMBASE, CENTRAL, LILACS and Chinese Medical Retrieval System search strategies.

Data collection and analysis

Selection of studies

Two review authors scrutinised titles and abstracts identified from the register. The review authors obtained the full text of all potentially relevant studies for independent assessment. Three review authors scrutinised all possible published and unpublished trials for inclusion. We resolved any disagreement by discussion.

Data extraction and management

Two review authors extracted data on participants, methods, interventions, outcomes and results independently and then entered the data into Review Manager (RevMan 5). We obtained missing data from the study authors whenever possible. We extracted data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance with the protocol, and whether or not the participant was subsequently deemed ineligible or otherwise excluded from treatment or follow-up, so that the data could be analysed on an intention-to-treat basis. We resolved disagreement by discussion.

Assessment of risk of bias in included studies

Two review authors (NC, MZ) assessed the risk of bias in each trial. The assessment of risk of bias took into account security of randomisation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and any other potential sources of bias. These items were assessed by two authors independently according to the Cochrane Collaboration standard scheme (Higgins 2008). All included trials were judged for each item. In all cases 'Yes' indicated a low risk of bias, 'No' a high risk of bias and 'Unclear' that there was insufficient detail to assess risk of bias or the entry was not relevant to the study. We resolved disagreement by discussion with reference to a third author if necessary.

Data synthesis

We used RevMan 5 software for the statistical analysis and reported data according to the Cochrane Collaboration criteria. Where meta-analysis was possible, results of clinically and statistically homogeneous trials were pooled to provide estimates of the efficacy. We planned to analyse all the primary and secondary outcomes under consideration. For dichotomous outcomes, the results were expressed as risk ratios (RRs), while for continuous outcomes means were compared and weighted mean differences (WMDs) were calculated, all with 95% confidence intervals (CIs). To avoid unit-of-analysis error resulting from combining results of more than one time point for each study in a standard meta-analysis, we evaluated outcomes based on the periods of follow-up (six months after disease onset). For studies that compared more than two intervention groups, we selected the relevant pair of intervention groups to include in the analyses.

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses:

1. Treatment started sooner or later after onset of herpes zoster (24 hours or less after onset; more than 24 hours up to 72 hours after onset and more than 72 hours after onset).

2. Younger and older (adults 49 years of age or less; adults aged 50 years or more).

Sensitivity analysis

We assessed heterogeneity among trials using the Chi^2 test with a 10% level of statistical significance ($P < 0.1$) and $I^2 > 50\%$ (Higgins 2002; Higgins 2003). When significant heterogeneity was present, we planned to undertake sensitivity analyses by repeating the calculation after omitting the trials which had a high risk of bias. We used a fixed-effect model for meta-analysis unless unexplained heterogeneity was identified when we planned to use a random-effects analysis. For trials that were clinically heterogeneous or provided insufficient information for pooling, a descriptive analysis was performed.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.
See Tables: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

For the 2010 update, the electronic searches retrieved a large number of references: four from the CENTRAL database, 490 from MEDLINE, 552 from EMBASE, none from LILACS, and 966 from the Chinese Biomedical Retrieval System. After scrutinising these titles and abstracts, we selected 40 possible randomised controlled trials: 35 were the same as those in the first version of this review. Five additional potentially relevant trials (Jiang 2008; Shi 2008; Zhou 2008; Song 2009; Yang 2010) were found during the search for the 2010 update. No other new trials were found by searching other sources. Further checking excluded 30 trials (see Characteristics of excluded studies): Two trials (Benoldi 1991; Keczkes 1980) compared corticosteroids with other treatment. Sixteen trials were found not to be RCTs by contacting the authors (Cui 2002; Hao 2002; Huang 2004; Jiang 2008; Ma 2002; Li 2000; Li 2002; Lin 2005; Ma 2000; Shi 2008; Song 2009; Tang 2004; Yang 2010; Zhang 2003; Zhou 2000; Zhou 2008). In seven trials participants received mismatched therapy in dosage, course of treatment or basal medication between corticosteroids and control groups (Guo 2001; Jiang 2005; Yin 2004; Yin 2005; Yang 2000; Zhang 2004; Zheng 2004). Four trials defined PHN as pain persisting at the site of shingles two weeks after the onset of the acute rash (Chang 2004; Liu 2003; Liu 2005; Yang 2002), and another trial defined PHN as pain persisting one week after total decrustation (Liao 2005); the follow-up of each of these studies was less than one month. Five studies are currently awaiting assessment: four trials included participants whose course of disease from onset of herpes zoster to start of treatment exceeded seven

days (Lin 2002; Wang 2004; Xu 1999; Zhang 2005). One trial did not clarify the exact course of disease from onset of herpes zoster to receipt of treatment (Hu 2001). We contacted the authors of the five studies awaiting assessment by mail, but no reply was obtained. Another article (Levinson 1985), which was classified as a study awaiting assessment in the first version of this Cochrane review, was a review of the previous studies; although the authors said they were investigating the feasibility of a multicentre trial in this field, we have not found any subsequent relevant trial reports , so we have removed from studies awaiting assessment.

Five trials (Clemmensen 1984; Eaglstein 1970; Esmann 1987; Whitley 1996; Wood 1994a) fulfilled the selection criteria (see Characteristics of included studies).

For the 2010 update we did not find any new trials for inclusion. Other forms of administration of corticosteroids such as epidural (van Wijck 2006) and paravertebral (Ji 2009) injections were investigated, but did not meet the inclusion criteria of the protocol for the present review. Although five more trials published in the last two years were found in the Chinese databases searched, they were all excluded mainly because their participants were not truly randomly assigned to groups.

Trial design

The included trials were all randomised, double-blind, placebo-controlled parallel studies. Two of these were performed in a single centre (Clemmensen 1984 conducted in Denmark; Eaglstein 1970 conducted in Miami dermatology inpatient service) and the others were performed in multiple centres (Esmann 1987 conducted in Aarhus and Copenhagen, Denmark; Whitley 1996 conducted in 15 university hospitals or affiliated clinics in USA; Wood 1994a conducted in four centres in the United Kingdom).

Participants

A total of 787 participants were enrolled in the five included studies. Four trials (Clemmensen 1984; Eaglstein 1970; Esmann 1987; Whitley 1996) reported the range of ages, 16 to 91 years old. Four trials (Clemmensen 1984; Esmann 1987; Whitley 1996; Wood 1994a) stated the gender distribution and mean age of participants (male 307, female 427). All of the five trials defined explicit inclusion criteria. Among them, one trial (Eaglstein 1970) included participants with early, severely painful zoster; four trials (Clemmensen 1984; Esmann 1987; Whitley 1996; Wood 1994a) included participants with herpes or pain of different grades of severity. One trial (Esmann 1987) included participants aged at least 60 years, and onset of herpes zoster less than 96 hours before admission. One trial (Whitley 1996) included immunocompetent adults older than 50 years of age who fell ill less than 72 hours before study enrolment. One trial (Wood 1994a) included adults who fell ill less than 72 hours before study enrolment. All five included trials also defined explicit exclusion criteria. They excluded participants with peptic ulcer, psychosis, malignant disease, hypertension, diabetes, cardiac insufficiency, adrenocortical disease, tuberculosis, lymphomas, leukaemias, bacterial infections, pregnancy, or those who were on corticosteroid treatment. The time of onset to start treatment was 0 to 7 days for four included trials (Clemmensen 1984; Esmann 1987; Whitley 1996; Wood 1994a). One trial (Eaglstein 1970) only stated the mean time was five days, and more details could not be obtained.

Interventions

The treatment regimens varied between studies (see Characteristics of included studies). Two trials (Eaglstein 1970; Clemmensen 1984) compared corticosteroids with placebo. One trial used triamcinolone orally 16 mg three times daily for seven days, 8 mg three times daily for seven days, and 8 mg twice daily for seven days (Eaglstein 1970). One trial administered corticosteroid orally or adrenocorticotropic hormone (ACTH) intramuscularly (Clemmensen 1984). Prednisone was given in doses of 45 mg daily during the first week, 30 mg daily during the second week, and 15 mg daily tapered to zero during the third week. ACTH (Synacthen depot, SD, 1 mg) was given intramuscularly three times a week (Monday, Wednesday, Friday) amounting to a total of seven injections. Placebo tables or injections indistinguishable from the active medication were used (Clemmensen 1984). Three trials used acyclovir in combination with corticosteroids versus acyclovir in combination with placebo (Esmann 1987; Whitley 1996; Wood 1994a). One trial used 800 mg acyclovir orally five times daily for seven days and coded tablets containing either prednisolone or calcium lactate for 21 days. The dose of prednisolone was 40 mg daily for seven days, 30 mg for four days, 20 mg for three days, 10 mg for four days, and finally 5 mg for three days (Esmann 1987). One trial used prednisone or a matched placebo orally, 60 mg/d for days one to seven, 30 mg/d for days eight to 14, and 15 mg/d for days 15 to 21 (Whitley 1996). Acyclovir or a matched placebo was administered orally as 800 mg 5 x daily for 21 days. Matched medications were identical in taste and appearance. The four treatment regimens given were acyclovir plus prednisone, acyclovir plus prednisone placebo, prednisone plus acyclovir placebo, and placebos for both acyclovir and prednisone (Whitley 1996). Another trial administered acyclovir 800 mg orally five times daily, beginning on day 0 (Wood 1994a). The participants in the groups assigned to seven days of acyclovir therapy (with or without corticosteroid) received matching placebo beginning on day seven. Prednisolone was administered according to the following schedule: on days 0 through six, 40 mg per day; days seven through 10, 30 mg per day; days 11 through 14, 20 mg per day; days 15 through 18 ,10 mg per day; and days 19 through 21, 5 mg per day (total dose 535 mg). Prednisolone was given as 5 mg tablets. The participants in the groups not receiving corticosteroid received matching placebo tablets. The four treatment regimens given were acyclovir for seven days with corticosteroids, acyclovir for seven days without corticosteroids, acyclovir for 21 days with corticosteroids, and acyclovir

for 21 days without corticosteroids (Wood 1994a). All trials followed the participants for at least six months, or until the postherpetic neuralgia ended or the participant no longer returned. One trial monitored all participants for three years (Eaglstein 1970).

Outcome measures

The outcome measures used differed between trials. Four trials reported the duration of PHN or presence of PHN at six months after the onset of the acute herpetic rash (Eaglstein 1970; Esmann 1987; Whitley 1996; Wood 1994a). Two trials did not provide separate information on the number of participants with PHN at six months, and were therefore not included in the meta-analysis (Whitley 1996; Wood 1994a). All five included trials did not report, as a separate outcome, pain severity measured by a validated visual analogue scale or numerical descriptive scale after three, six and 12 months or the quality of life measured with the short form 36 questionnaire (SF-36) after six months. All five included trials reported adverse events during or within two weeks after stopping treatment. Adverse events were categorised as serious or not serious.

Risk of bias in included studies

See: 'Risk of bias table' of each included study

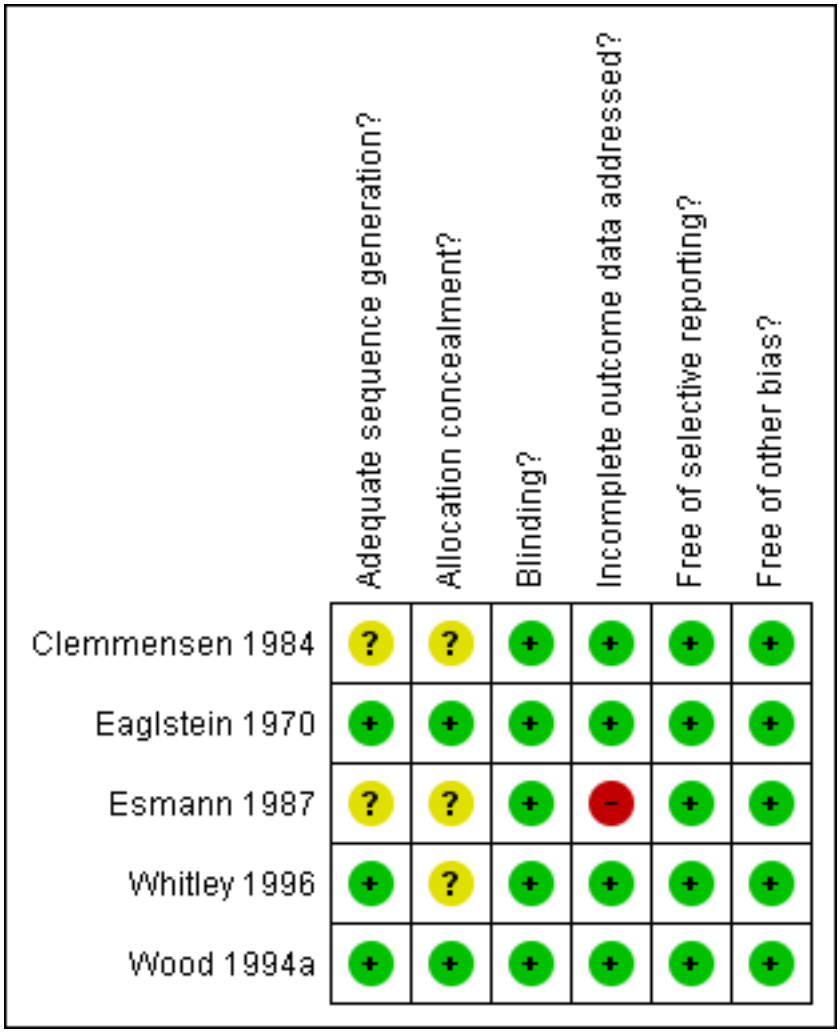
All included trials were randomised, double-blind, placebo-controlled parallel studies. The method of randomisation was reported in three included trials (Eaglstein 1970; Whitley 1996; Wood 1994a). The Eaglstein study (Eaglstein 1970) used randomisation with a centralised code generated at a pharmacy. A supply of medication for each participant was assigned a different code number and distributed to the participants; the code of each patient was opened after a three year follow-up. The Whitley and Wood studies both used a computer-generated randomisation code to randomly assign participants; in Wood 1994a the randomisation code was stratified by study centre to assign patients in blocks of eight to either group, so that allocation concealment might be performed), but the method of allocation concealment in Whitley 1996 was unclear. Clemmensen 1984 and Esmann 1987 did not describe the method of randomisation, and it was not clear from the reports if there was adequate allocation concealment in either study. The five included trials were all double-blind, using placebo in the control group. One of these trials used lactose as placebo (Eaglstein 1970), another used calcium lactate (Esmann 1987), and the other three studies only stated placebo tablets indistinguishable from the active medication, but did not describe their composition (Clemmensen 1984; Whitley 1996; Wood 1994a). Three of the five trials (Esmann 1987; Whitley 1996; Wood 1994a) included acyclovir as routine treatment. All trials considered baseline clinical features. In four trials the baseline clinical features were similar between groups (Clemmensen 1984; Esmann 1987; Whitley 1996; Wood 1994a). In one trial baseline differences were not described (Eaglstein 1970), but the authors reported no serious imbalances in baseline prognostic factors between groups.

All five included studies reported the time of follow-up; three used six months (Esmann 1987; Whitley 1996; Wood 1994a), one ten months (Clemmensen 1984), and one three years (Eaglstein 1970). In one study (Esmann 1987) six patients were withdrawn, but it was unclear whether the lack of compliance was due to inefficacy or side effects.The group those patients were first assigned to was not specified, so bias from incomplete outcome data is possibly an issue in this study. The other four studies all reported information about follow-up and drop out, and described the reasons for drop out clearly. Only one study claimed that an intention-to-treat analysis was used (Whitley 1996), the other four included studies did not state whether or not the analysis was intention-to-treat, but there was sufficient information in the other trial reports (Clemmensen 1984;Eaglstein 1970; Wood 1994a) to restore them to the correct group and perform an intention-to-treat analysis in our review.

For each included study, outcomes listed in the methods section were all reported. Publication bias should be taken into account, since most of the included and excluded studies were published in English or Chinese, although we have attempted to do our best to search all probable literature without any language restrictions and have contacted investigators to get more information. These included studies used different cut-off times to definite PHN, so although we clearly stated PHN was pain persisting, or recurring, at the site of shingles at least one month after the onset of the acute rash, we have not restricted inclusion to studies using the same definition in order not to introduce more missing data.

According to the new summary risk of bias assessment (Higgins 2008), two (Eaglstein 1970; Wood 1994a) of the trials were rated as good quality (low risk of bias), two (Clemmensen 1984;Whitley 1996) as unclear (unclear risk of bias), and one (Esmann 1987) as poor (high risk of bias) (Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids for acute herpes zoster to prevent postherpetic neuralgia

Primary outcome measure

Presence of PHN six months after the onset of the acute herpetic rash

One trial comparing triamcinolone with placebo (Eaglstein 1970) provided data on the presence of PHN six months after the onset of the acute herpetic rash. There was no significant difference in the number of participants with PHN six months after the onset of the acute herpetic rash between those in the corticosteroids group (2/15,13.3%) and those in the placebo group (2/20, 10.0%). However the wide confidence interval meant we could not rule out significant benefit or harm (RR 1.33, 95% CI 0.21 to 8.41). This study also reported the presence of PHN at other time points during follow-up, including one and four months after the onset, which were also commonly used to evaluate incidence of PHN. The presence of PHN was not statistically different between groups as well (9/15 versus 14/20 at one month, P = 0.55; 2/15 versus 4/20 at four month, P = 0.61). Another trial comparing prednisolone plus routine treatment with placebo plus routine treatment (Esmann 1987) provided data for our primary

outcome. The trial compared acyclovir plus corticosteroids with acyclovir plus placebo. The presence of PHN six months after the onset of the acute herpetic rash following corticosteroids plus antiviral agents (9/42, 21.4%) was not significantly different from its presence for placebo plus antiviral agents (9/37, 24.3%) (RR 0.88, 95% CI 0.39 to 1.98). In the updated version of this review we conducted a meta-analysis combining relevant data from the above two trials with a total of 114 participants, and the results showed that oral corticosteroids did not play a part in preventing PHN six months after the herpes onset (RR 0.95, 95% CI 0.45 to 1.99; P = 0.89; Analysis 1.1; Figure 2). The Clemmensen study (Clemmensen 1984) used a cut-off time of six weeks for defining PHN, concluding that prednisone did not decrease the incidence of PHN. Since the numbers of patients with PHN six months after the rash onset could not be obtained, these data were not included in any meta analysis for effects of corticosteroids (Summary of findings for the main comparison).

Two other trials provided relevant data for this outcome although not in a format which permitted inclusion in our meta-analysis. In a trial with 201 participants (Whitley 1996), a Cox regression model analysis of the main effect of prednisone compared with no prednisone showed no significant difference in the time to cessation of zoster-associated pain (RR 1.26, 95% CI 0.91 to 1.75). From their Cox regression model, we used the generic inverse variance approach to calculate the main effect of prednisone compared with no prednisone and confirmed that there was no significant difference in the time to cessation of zoster-associated pain (RR 1.11, 95% CI 0.96 to 1.27) (Analysis 1.2; Figure 3). In the trial with 400 participants of whom 349 completed the study (Wood 1994a), the investigators did not detect significant differences between any of the treatment groups in the time to complete cessation of pain. The median time to cessation of pain was 147 and 120 in the 7-day and 21-day acyclovir without a corticosteroid groups, and 146 and 120 in the two acyclovir with corticosteroids groups respectively. Thus the results of both these large trials agreed with the conclusion from the meta-analysis of the two smaller trials that corticosteroids did not significantly affect the presence of PHN after six months.

Figure 2. Forest plot of comparison: 1 Corticosteroids vs placebo or no treatment, outcome: 1.1 The presence of PHN six months after the onset of the acute herpetic rash.

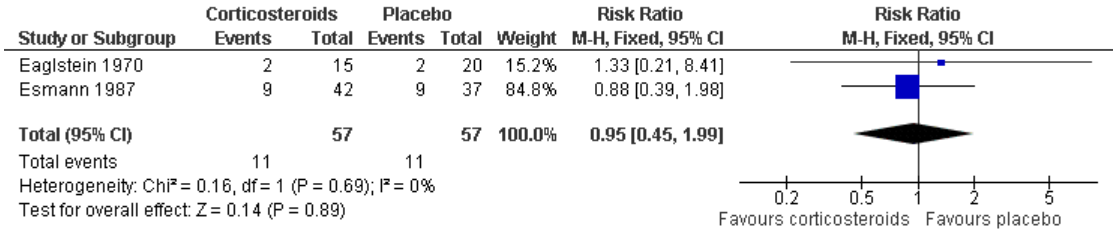
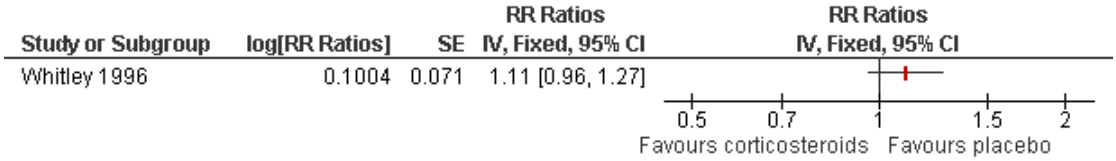


Figure 3. Forest plot of comparison: 1 Corticosteroids vs placebo or no treatment, outcome: 1.2 The main effect of prednisone compared with no prednisone on six months evaluation of pain (generic inverse variance).



Secondary outcome measures

(1) Pain severity measured by a validated visual analogue scale or numerical descriptive scale after three, six and 12 months

Four included trials (Clemmensen 1984; Eaglstein 1970; Esmann 1987; Wood 1994a) evaluated pain intensity after using corticosteroids to treat acute herpes zoster, but three of them (Clemmensen 1984; Eaglstein 1970; Wood 1994a) recorded such data only during the first month and they used different pain evaluation methods, so we were not able to include the data in a meta-analysis even when attempting to convert outcomes to dichotomous data. The Clemmensen study graded pain from 0 (no pain) to 3 (insufferable pain); there was no significant difference in mean pain score between prednisone and placebo during the 21 day treatment period, and the score was significantly lower in the ACTH group during the first four days of the trial (P = 0.02 to 0.03) but not after (Clemmensen 1984). One trial reported that in participants more than 60 years old, pain resolved spontaneously but more rapidly with corticosteroids (Eaglstein 1970). In the Wood trial (Wood 1994a), the reduction in pain score was significantly larger in the corticosteroids groups than the no-corticosteroids groups on days 7 and 14 (P < 0.01). Only one trial reported at six months, 18 participants had pain, of whom 15 had light, two had moderate and one had severe pain. Among them nine had received prednisone and nine placebo but the severity of pain was not reported by group (Esmann 1987).

(2) Quality of life measured with the short form 36 questionnaire (SF-36) after six months

None of the trials reported separate data on quality of life measured with the short form 36 questionnaire (SF-36) after six months.

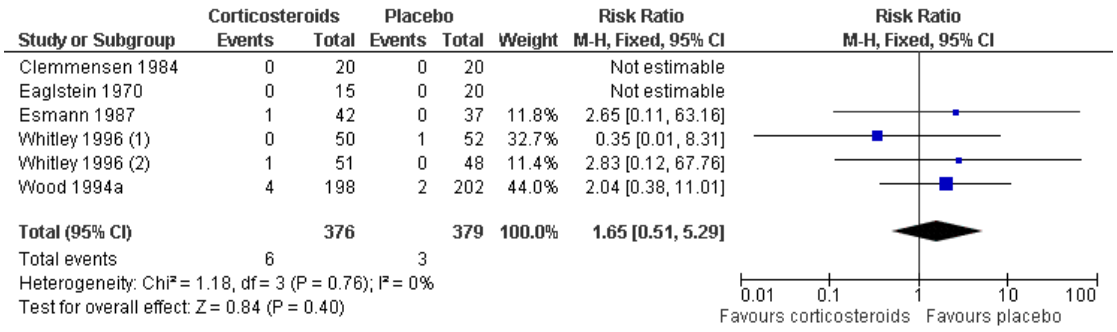
(3) Adverse events during or within two weeks after stopping treatment

Adverse events were categorised as serious or not serious. Serious adverse events were those which were life-threatening, required or prolonged hospitalisation, or caused death. Details for individual studies have been given in the 'Characteristics of included studies' table.

(a) Serious adverse events

Two of the included trials explicitly recorded the absence of serious adverse effects attributable to the experimental treatment (Clemmensen 1984; Eaglstein 1970). The other three trials all reported several serious adverse events during or within two weeks after stopping treatment, including acute cardiac insufficiency (Esmann 1987), myocardial infarction (Whitley 1996), pneumonia or bronchopneumonia (Whitley 1996; Wood 1994a), chest infection (Wood 1994a), haematemesis (Wood 1994a) and death from other unspecified reasons (Wood 1994a). In the meta-analysis, the incidence of serious adverse events for corticosteroids (6/376, 1.6 %) was not significantly different from that for placebo (3/379, 0.8%) (RR 1.65, 95% CI 0.51 to 5.29, P = 0.40; Analysis 1.3; Figure 4).

Figure 4. Forest plot of comparison: 1 Corticosteroids vs placebo, outcome: 1.3 Serious adverse events.

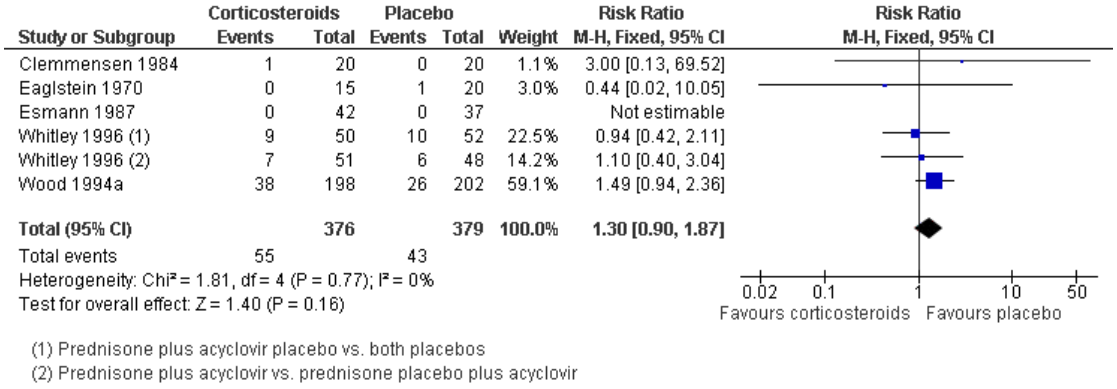


(1) Prednisone plus acyclovir placebo vs. both placebos
(2) Prednisone plus acyclovir vs. prednisone placebo plus acyclovir

(b) Non-serious adverse events

All five trials reported details of non-serious adverse events, including clinical manifestation or laboratory results, number of patients experiencing each adverse event, and their distribution between groups. The most frequently reported non-serious adverse events were gastrointestinal symptoms (such as dyspepsia, nausea vomiting and diarrhoea), dizziness, headache, sweats, rash, edema, hyperglycaemia, and increase of serum aspartate glutamyltransferase. In our meta-analysis of data from the five trials, (Analysis 1.4; Figure 5), the overall incidence of non-serious adverse events for corticosteroids (55/376, 14.6%) was not statistically significant compared to placebo (43/379, 11.3%) (RR 1.30, 95% CI 0.90 to 1.87, P = 0.16).

Figure 5. Forest plot of comparison: 1 Corticosteroids vs placebo, outcome: 1.4 Non-serious adverse events.



(1) Prednisone plus acyclovir placebo vs. both placebos
(2) Prednisone plus acyclovir vs. prednisone placebo plus acyclovir

Subgroup analyses

1. Time from onset of herpes zoster to start of treatment (24 hours or less after onset, more than 24 hours up to 72 hours after onset and more than 72 hours after onset);

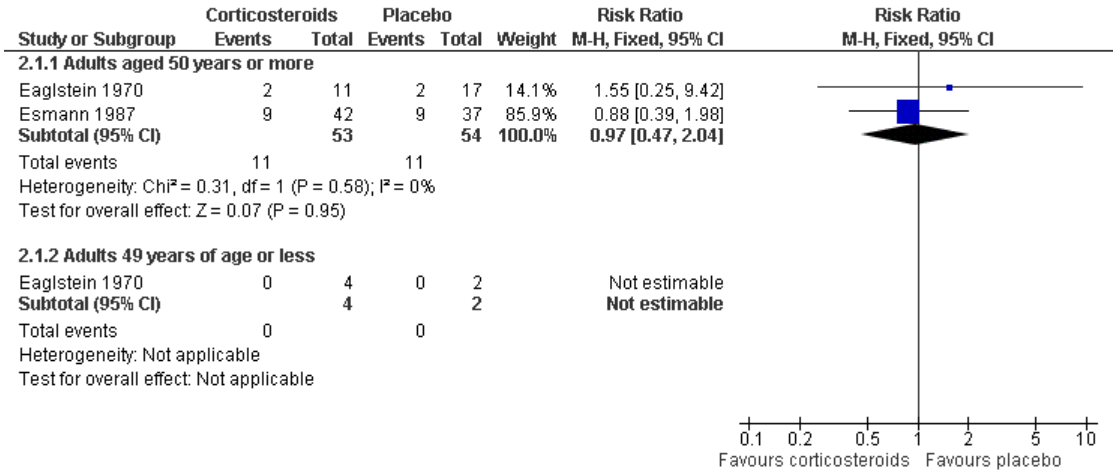
This information was not available from the published reports.

2. Younger and older (adults 49 years of age or less; adults aged 50 years or more).

(a) Adults aged 50 years or more

The Eaglstein study (Eaglstein 1970) reported duration of pain for each patient in bar charts, which clearly showed the age of each participant. Two other trials (Esmann 1987; Whitley 1996) only enrolled patients aged more than 60 or 50 years old. So a subgroup analysis involved only adults aged 50 years or more was potentially possible for these three trials. Unfortunately the Whitley study was not included in the meta-analysis since detailed numbers of events could not be extracted from this article. Thus in two trials (Eaglstein 1970; Esmann 1987) including 107 participants aged 50 years or more, the presence of PHN six months after the onset of the acute herpetic rash in the corticosteroids group (11/53, 20.8%) was similar to that in the placebo group (11/54, 20.4%) (RR 0.97, 95% CI 0.47 to 2.04) (Analysis 2.1; Figure 6).

Figure 6. Forest plot of comparison: 2 Sub-group analysis, outcome: 2.1 The presence of PHN six months after the onset of the acute herpetic rash.



The Clemmensen study (Clemmensen 1984) reported 33 participants in the group of patients aged over 55 years, of whom nine developed PHN (four in the prednisone group, one in the placebo group, and four in the other treatment group) without significant differences between groups. However, the study defined PHN using a six-week cut-off time and only reported the mean duration of PHN as 4.2 months (range 1.5 to 10.0 months), so we were not able to obtain the separate data on participants with PHN after six months follow-up.

(b) Adults 49 years of age or less

In one trial, with six participants (Eaglstein 1970), none developed PHN after six month follow- up. In the Clemmensen study (Clemmensen 1984) none of the 22 participants of 55 years of age or less developed PHN (the mean duration of PHN as 4.2 months). Relevant data could not be obtained from the other trials. One of the participants in the Eaglstein study was not included in either the younger or older subgroup, because she was withdrawn because of possible side effects. Her age was not reported in the article (Eaglstein 1970).

Sensitivity analyses

Heterogeneity amongst trials was assessed for each comparison, but no significant heterogeneity (I^2 > 50%) was present. Furthermore, although a trial of poor quality was included in the meta-analyses, the results of each included trial were all similar with no significant differences in outcomes relevant to this review. Therefore we did not undertake any sensitivity analysis.

DISCUSSION

(1) Clinical therapeutic effect

Our aim was to review the evidence from RCTs of the effectiveness and safety of corticosteroids in preventing PHN. Only five studies examining the prevention effects of corticosteroids in a total of 787 participants were suitable for this review. This is a relatively small number in relation to the known variability in outcome of PHN.

The meta-analysis of two trials which provided data for our primary outcome measure showed no significant difference in the number of participants with PHN six months after the onset of the acute herpetic rash between those in the corticosteroid group and those in the placebo group. There was no significant difference in time to cessation of pain in two larger trials, one with 201 and one with 359 participants (Whitley 1996; Wood 1994a). Established PHN may be intractable and lead to considerable disability in social and domestic activities. Pain evaluation is the key step to controlling neuropathic pain. Doctors must make a detailed and full-scale pain evaluation during the period of treatment and follow-up including pain character, intensity, position and scope. The most used evaluation methods are the validated visual analogue scale (VAS) or numerical descriptive scales (NRS). Four of the trials included in this review evaluated pain intensity changes but used different pain evaluation methods, so we were unable to combine the data in our meta-analysis. Two trials (Esmann 1987; Clemmensen 1984) reported that corticosteroid treatment did not give additional pain relief during the three or six month follow-up. One trial (Eaglstein 1970) reported that pain tended to resolve

spontaneously without therapy but more rapidly with corticosteroid therapy, but this trial only included 35 participants.
Despite the lack of benefit in terms of reduction of PHN which was the focus of this review, there is some evidence of a beneficial effect on short-term outcomes. A trial with 359 participants (Wood 1994a) showed that pain intensity after two and three weeks had reduced from baseline significantly more in those who received corticosteroids than in those who did not. Another trial with 201 participants (Whitley 1996) showed significantly faster recovery with corticosteroids than without. On evaluation after one month with the Cox regression model, the main effect of prednisone compared with no prednisone was significant for all four outcomes reported:

1. time to cessation of acute neuritis (RR 2.28, 95% CI 1.35 to 3.86).
2. time to return to uninterrupted sleep (RR 1.65, 95% CI 1.14 to 2.41).
3. time to return to 100% usual daily activity (RR 1.74, 95% CI 1.21 to 2.51)
4. time to total cessation of analgesic therapy (RR 2.25, 95% CI 1.42 to 3.54).

The results of these two papers suggest that corticosteroids may have a significant effect in accelerating healing and reducing acute zoster pain. This conclusion differs from the lack of effect of corticosteroids on the persistence of PHN and suggests that the relationship between acute inflammation and pain and PHN is not simple.

(2) Adverse events

All five included trials reported adverse events, but these were not significantly more common in corticosteroid than placebo participants.

(3) Subgroup analyses

Although the most established risk factor for PHN is age, accurate predictors for PHN have not been defined (Johnson 2003). We conducted subgroup analyses according to age of participants but did not find significant benefit either in those older than 50 or those younger. Small numbers make this conclusion very uncertain. There was a lack of sufficient detail to permit extraction of all required data concerning most subgroups of interest. In the absence of a significant effect in the primary outcome measures and the fact that individual trials were too small to detect moderate effects, more extensive subgroup analysis would have been unreliable. We hope that publication of this review will encourage authors of future PHN prevention trials to collect and publish data which will allow the analysis of subgroups in subsequent systematic reviews.

(4) Outcome measures

In the trials reviewed, the outcome measures involved crude clinical endpoints or a simple pain scale which may be insufficiently responsive to detect meaningful clinical effects. None of the trials reported separate data on pain severity measured by validated visual analogue scales or numerical descriptive scales after three, six or 12 months. However even the results of these scales are affected by difficulties in standardisation which make it difficult to draw useful conclusions.
None of the trials reported separate data on quality of life measured with the short form 36 questionnaire (SF-36) after six months.The short form 36 questionnaire is used to assess physical functioning, bodily pain, vitality, social functioning, emotional role and mental health but can also be used for evaluating quality of life of pain patients (Ware 1998). None of the four trials used this questionnaire to assess the quality of life among the pain patients, and only one trial evaluated aspects of quality of life (Whitley 1996). Future randomised controlled trials should monitor long-term quality of life regularly which could allow better evaluation of the efficacy of corticosteroids. Regular monitoring of participants' quality of life would improve understanding of the natural progression of PHN with respect to its impact on the physical, emotional and social well-being of patients.
No trial has incorporated cost-effectiveness calculations.

(5) Future trials

The meta-analysis of two small studies (Eaglstein 1970; Esmann 1987) and the analysis of another two large studies (Wood 1994a; Whitley 1996) showed that corticosteroids did not reduce pain at six months after the onset of the acute rash more than the control group. However the results of the Wood and Whitley studies suggested that corticosteroids may reduce the acute pain in herpes zoster and may improve quality of life.
The relationship between acute inflammation and pain and PHN is complicated. The effect of corticosteroids is not clear at different stages in the transition from acute pain to PHN. Dworkin et al. have recommended the use of systemic corticosteroids as soon as possible after diagnosis of herpes zoster for patients with at least moderately severe pain and no contraindications, and that these should be initiated only in combination with antiviral therapy (Dworkin 2007). However, this recommendation is based on expert opinion and the evidence for the effect of corticosteroids on preventing PHN at six months would not support this recommendation. However trials addressing short-term pain relief with corticosteroids are lacking. If they were performed they should also include a long-term follow up to assess the transition from short-term to long-term pain. Further high quality randomised controlled trials using validated and generally accepted outcome measures should be considered for both short and long-term pain prevention and treatment in PHN. In a condition where the nat-

ural course is spontaneous recovery in the majority of cases, the number of participants has to be large enough to give the study the power to detect clinically relevant improvements.

AUTHORS' CONCLUSIONS

Implications for practice

Short courses of corticosteroids do not result in significantly more adverse events in participants with acute herpes zoster but they are ineffective in preventing postherpetic neuralgia.

Implications for research

Moderate quality evidence does not support the use of corticosteroids in acute herpes zoster infection for preventing postherpetic neuralgia. However large trials with sufficient power to detect a meaningful difference which include validated and approved pain outcomes have not been performed. Further high quality studies to assess the effect of corticosteroids on both short-term pain and longer term PHN are required. This may provide information about the mechanisms of transition from acute pain to long-term PHN.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Clemmensen 1984

Methods	Single centre randomised controlled trial, double-blind, placebo-controlled, parallel-group study (methods not described).
Participants	60 patients (33 males and 22 females) within seven days of onset of HZ. Ages ranged from 16 to 86 years, 33 were 55 years or older. Among them 20 patients received intramuscular Synacthen depot. 5 patients dropped out. Patients excluded were (1) those with duration of symptoms (pain and/or cutaneous signs) beyond 7 days; (2) those below 16 years of age; (3) those with generalised HZ (more than 50 vesicles outside the affected dermatome); (4) those with a history of, or current malignant disease; (5) those undergoing treatment with cytostatics and corticosteroids; (6) those with a history or findings of peptic ulcer, psychosis, cardiac decompensation, hypertension, diabetes mellitus, adrenocortical disease or with symptoms of osteoporosis; (7) those who were pregnant.
Interventions	Synacthen depot (SD): SD 1 mg was given intramuscularly three times a week (Monday, Wednesday, Friday) amounting to a total of seven injections. Prednisone: prednisone was given orally in doses of 45 mg daily during the 1st week, 30 mg daily during the 2nd week, and 15 mg daily tapered to zero during the 3rd week. Placebo tablets or injections indistinguishable from the active medication were used. Comparison treatment placebo.
Outcomes	Primary: nine patients developed PHN. They all belonged to the group comprising patients above 55 years. The mean duration of PHN at the final evaluation was 4.2 months (range 1.5 to 10 months). Four patients were found in the SD group (4/17, 23.5%), four in the prednisone group (4/19, 21%), and one in the placebo group (1/19, 5.3%). Secondary outcome: No serious adverse events developed. Non serious adverse events: one in the prednisone group (increasing blood sugar); three in the SD group (uncomfortable dizziness and moderate periorbital oedema).
Notes	Conducted in Denmark

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described.
Allocation concealment?	Unclear	Method of allocation concealment was not described.

Clemmensen 1984 (*Continued*)

Blinding? All outcomes	Yes	It was stated that a "double-dummy" administration technique was used: matched oral and/or parenteral placebo was given to each patient.
Incomplete outcome data addressed? All outcomes	Yes	5 patients dropped out, one patient in the prednisone group (because of increasing blood sugar), one patient in the placebo group (discontinued by the patient without specific reason), three patients in the SD group (two patients developed uncomfortable dizziness and one patient moderate periorbital oedema).
Free of selective reporting?	Yes	Outcomes listed in the methods section were all reported.
Free of other bias?	Yes	No other potential bias was found.

Eaglstein 1970

Methods	Single centre, randomised, double-blind, placebo-controlled parallel design.
Participants	35 patients with early, severely painful zoster were admitted to the dermatology inpatient service. Ages ranged from 21 to 91 years, 24 of them being older than 59 years of age. One patient dropped out. No patients with hypertension, tuberculosis, lymphoma, leukaemia, bleeding peptic ulcers, diabetes, cardiac disease, or bacterial infections were included.
Interventions	Patients were treated with unmarked red capsules containing either 8 mg of triamcinolone or lactose. The patients received two capsules three times daily (48 mg/day) for 7 days, and one capsule 3 times daily (24 mg/day) for 7 days, and one capsule twice daily (16 mg/day) for 7 days.
Outcomes	Primary outcome (the presence of PHN six months after the onset of the acute herpetic rash): two in the triamcinolone group; two in the placebo group. Secondary outcome: No serious adverse events developed. Non serious adverse events: one in the placebo group (a sudden increase in the blood pressure).
Notes	Conducted in Miami dermatology inpatient service

Risk of bias

Item	**Authors' judgement**	**Description**

Eaglstein 1970 (*Continued*)

Adequate sequence generation?	Yes	Random numbers were used; each patient was assigned a different code number and distributed to a group in a random fashion
Allocation concealment?	Yes	The code for each patient was opened after a three-year follow-up and evaluation.
Blinding? All outcomes	Yes	Patients were treated with unmarked red capsules prepared by the hospital pharmacy.
Incomplete outcome data addressed? All outcomes	Yes	Only one patient in the controlled group dropped out after five days because of a sudden increase in her blood pressure.
Free of selective reporting?	Yes	Outcomes listed in the methods section were all reported.
Free of other bias?	Yes	No other potential bias was found.

Esmann 1987

Methods	Multicentre randomised, double-blind, placebo-controlled parallel design. Number of losses to follow up: all patients were evaluated at week 26 except for one from the prednisolone group, who was last seen at week 10. She had not had pain since day 5.
Participants	84 patients (25 males and 53 females) within four days of onset of HZ. Age at least 60 years. Mean age: intervention group 72.8 (SD 7.5); control group 71.4 (SD 8.1). Patients were excluded if they were immunocompromised; had pituitary or adrenal dysfunction, diastolic blood pressure above 105 mm Hg on entry day, signs of cardiac insufficiency, insulin dependent diabetes, bacterial infections, bleeding peptic ulcers, severe mental confusion, serum creatinine 150 mmol; or were on corticosteroid treatment.
Interventions	800 mg acyclovir orally five times daily for 7 days and coded tablets containing either prednisolone or calcium lactate for 21 days. The dose of prednisolone was 40 mg daily for 7 days, 30 mg for 4 days, 20 mg for 3 days, 10 mg for 4 days, and finally 5 mg for 3 days.
Outcomes	Primary outcome (the presence of PHN six months after the onset of the acute herpetic rash): nine in the prednisone group; nine in the placebo group. Secondary outcome: Serious adverse events: one in the prednisone group (acute cardiac insufficiency). Non serious adverse events did not occur.
Notes	Conducted in Aarhus and Copenhagen, Denmark
Risk of bias	

Esmann 1987 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described.
Allocation concealment?	Unclear	Method of allocation concealment was not described.
Blinding? All outcomes	Yes	The trial report stated that double-blind method was used, and all patients were given coded tablets containing either prednisolone or calcium lactate.
Incomplete outcome data addressed? All outcomes	No	Six patients were withdrawn, either because the inclusion criteria could not be upheld upon subsequent scrutiny or because of lack of compliance during the first 1-2 weeks. One of the six patients dropped out because of a possible side effect of prednisolone, and she could be included in the intention-to-treat analysis. But whether the lack of compliance of the other patients was due to inefficacy or side effects, and which group those five patients were firstly assigned to, were not specified.
Free of selective reporting?	Yes	Outcomes listed in the methods section were all reported.
Free of other bias?	Yes	No other potential bias was found.

Whitley 1996

Methods	Multicentre randomised, double-blind, placebo-controlled parallel study with a 2 x 2 factorial design. (A computer-generated randomisation code randomly assigned patients to one of the four treatment groups. All research personnel remained blinded to drug assignment until the study was completed and the database was locked. All matched medications were identical in taste and appearance). 32 (16%) were lost to follow up: 14% (7 of 51) of acyclovir plus prednisone recipients,13% (6 of 48) of acyclovir plus prednisone placebo,18% (9 of 50) prednisone plus acyclovir placebo recipients, and 19% (10 of 52) of patients receiving two placebos.
Participants	208 immunocompetent patients older than 50 years of age who had localised herpes zoster that developed less than 72 hours before study enrolment. Five randomly assigned patients were not included in this analysis because they never received study medication; no case record forms were submitted. Two other patients were proven to have herpes simplex virus infection and thus were not included in the analysis. Of the 201 patients included in the analysis, 51 received acyclovir plus prednisone (24 males and 27 females,

	mean age 63), 48 received acyclovir plus prednisone placebo (21 males and 27 females, mean age 62), 50 received prednisone plus acyclovir placebo (26 males and 24 females, mean age 60), and 52 received acyclovir and prednisone placebo (25 males and 27 females, mean age 61). 32 patients were lost to follow-up. Exclusion criteria: patients who required immunosuppressive therapy; patients with cancer; women capable of conceiving and bearing a child; patients who had a history of hypertension (diastolic pressure >100 mm Hg) or were receiving antihypertensive therapy; patients with osteoporosis or insulin-dependent diabetes mellitus; patients who had received other antiviral drugs or immunoglobulin products within the 4 weeks before the study began; and patients with a history of glycosuria or hyperglycaemia.
Interventions	Prednisone or a matched placebo was given orally 60 mg/d for days 1 to 7, 30 mg/d for days 8 to 14, and 15 mg/d for days 15 to 21. Acyclovir or a matched placebo was administered orally as 800 mg 5 x daily, for 21 days. Matched medications were identical in taste and appearance. The four treatments regimens given were acyclovir plus prednisone, acyclovir plus prednisone placebo, prednisone plus acyclovir placebo, and placebos for both acyclovir and prednisone.
Outcomes	Primary outcome: Six-month evaluation of pain (time to cessation of zoster-associated pain): acyclovir plus prednisone compared with placebo (RR 1.56 95% CI 8.92 to 2.66); acyclovir plus prednisone placebo compared with placebo (RR 1.39 95% CI 0.84 to 2.32); prednisone plus acyclovir placebo compared with placebo (RR 1.26, 95% CI 0.72 to 2.21); main effect of prednisone: prednisone compared with no prednisone (RR 1.26, 95% CI 0.91 to 1.75). Secondary outcome: 1. One-month evaluation of quality of life: main effect of corticosteroids: prednisone compared with no prednisone (1) time to cessation of acute neuritis (RR 2.28, 95% CI 1.35 to 3.86). (2) time to return to uninterrupted sleep (RR 1.65, 95% CI 1.14 to 2.41). (3) time to return to 100% usual daily activity (RR 1.74, 95% CI 1.21 to 2.51) (4) time to total cessation of analgesic therapy (RR 2.25; 95% CI 1.42 to 3.54). 2. adverse events: Serious adverse events: one in the acyclovir plus prednisone group died of myocardial infarction on study day 26; Three patients (one receiving acyclovir plus prednisone placebo and two receiving prednisone plus acyclovir placebo) developed cutaneous dissemination. One in the placebo group developed bacterial pneumonia. Non serious adverse events: forty-two patients had one or two adverse events. 11 in the acyclovir plus prednisone group, 13 in the acyclovir plus prednisone placebo group, 12 in the prednisone plus acyclovir placebo group, 6 in the placebo group. They were gastrointestinal symptoms, especially nausea and vomiting, other reported adverse events included oedema; increased leukocyte counts; and altered platelet counts, bilirubin levels, or hepatic function test results.
Notes	Conducted in 15 university hospitals or affiliated clinics in USA. 32 patients dropped out: 7 in the acyclovir plus prednisone group, 6 in the acyclovir plus prednisone placebo group, 9 in the prednisone plus acyclovir placebo group, and 10 in the acyclovir and prednisone placebos. Patients discontinued therapy because of influenza, conjunctivitis or iritis, nausea and vomiting, complete resolution of disease,

Whitley 1996 (*Continued*)

	cutaneous dissemination, hyperglycaemia, and bacterial pneumonia.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Used a computer-generated randomisation code.
Allocation concealment?	Unclear	Method of allocation concealment was not described.
Blinding? All outcomes	Yes	All research personnel remained blinded to drug assignment until the study was completed and the database was locked. All matched medications were identical in taste and appearance.
Incomplete outcome data addressed? All outcomes	Yes	Missing data were equal among the treatment groups, and an intention-to-treat analysis was performed.
Free of selective reporting?	Yes	Outcomes listed in the methods section were all reported.
Free of other bias?	Yes	No other potential bias was found.

Wood 1994a

Methods	Multicentre randomised, double-blind, placebo-controlled parallel study. Number losses to follow up: 2 patients in 7-day acyclovir with corticosteroids; 3 patients in 7-day acyclovir without corticosteroids; 2 patients in 21-day acyclovir with corticosteroids; 3 patients in 21-day cyclovir without corticosteroids.
Participants	Adults over 18 years of age without immune dysfunction due to cancer or immunosuppressive therapy, who presented with a clinical diagnosis of herpes zoster as confirmed by one of the investigators and had a rash for 72 hours or less and at least moderate pain, were enrolled. A total of 400 patients were enrolled in the study. Ninety-nine patients were assigned to receive acyclovir for 7 days with corticosteroids (37 males and 62 females, mean age 59),101 to receive acyclovir for 7 days without corticosteroids (39 males and 62 females, mean age 58), 99 to receive acyclovir for 21 days with corticosteroid (39 males and 60 females, mean age 60), and 101 to receive acyclovir for 21 days without corticosteroid (38 males and 63 females, mean age 59). 51 patients were withdrawn. The following patients were excluded from the study: pregnant women and women of childbearing potential who were not adequately protected by contraception; patients with renal insufficiency (serum creatinine concentration, more than 1.8 mg per decilitre), hypertension (diastolic pressure, >110 mmHg), insulin-dependent diabetes, or a random blood glucose determination exceeding 216 mg per decilitre (12 mmol per litre)

Wood 1994a (*Continued*)

	; patients with a history of peptic ulceration, severe psoriasis, or hypersensitivity to acyclovir; and patients receiving barbiturates, anticonvulsant drugs, systemic corticosteroids, rifampicin, or specific antiviral therapy for the present infection.
Interventions	Acyclovir (800 mg orally) was administered five times daily, beginning on day 0. The patients in the groups assigned to seven days of acyclovir therapy (with or without corticosteroid) received matching placebo beginning on day 7. Prednisolone was administered according to the following schedule: on days 0 through 6, 40 mg per day; days 7 through 10, 30 mg per day; days 11 through 14, 20 mg per day; days 15 through 18,10 mg per day; and days 19 through 21, 5 mg per day (total dose 535 mg). Prednisolone was given as 5 mg tables.
Outcomes	Primary outcome: up to Month 6 to assess postherpetic neuralgia Time to complete cessation of pain median days (number of patients): 7-day acyclovir plus corticosteroid (146, 58); acyclovir 7 days without corticosteroids (147, 65); acyclovir 21 days with corticosteroids (120, 64); acyclovir 21 days without corticosteroids (120,64). Secondary outcomes: 1. serious adverse events; 7-day acyclovir plus corticosteroid (1,death); acyclovir 7 days without corticosteroids (0); acyclovir 21 days with corticosteroids (1, death;1, bronchopneumonia; 1, haematemesis) ; acyclovir 21 days without corticosteroids (1,death; 1, chest infection). 2. not serious adverse events: A higher incidence of adverse events was observed in the corticosteroid recipients (38 patients, or 19%) than in the recipients of acyclovir alone (26 patients, or 13%) (P > 0.1). Included dyspepsia, nausea, vomiting, diarrhoea, depression, dizziness, headache, paraesthesiae, hot flushes, sweats, oedema, hypertension.
Notes	Conducted in 4 clinical centres in the United Kingdom. 51 patients were withdrawn: 14 in acyclovir for 7 days with corticosteroid group, 10 in acyclovir for 7 days without corticosteroid group, 13 in acyclovir for 21 days with corticosteroid group, 14 in acyclovir for 21 days without corticosteroid group. Reasons were deviation from protocol, adverse events, loss to follow-up, no reason given, and death.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A computer-generated randomisation code was used.
Allocation concealment?	Yes	The randomisation code was stratified by study centre to assigned patients in blocks of eight to either group; it indicated that allocation concealment might be performed.

Wood 1994a (*Continued*)

Blinding? All outcomes	Yes	It was stated that it was a double-blind study, and the patients in the groups not receiving corticosteroid received matching placebo tablets.
Incomplete outcome data addressed? All outcomes	Yes	Withdrawals of patients and the reasons were balanced equally across all groups.
Free of selective reporting?	Yes	Outcomes listed in the methods section were all reported.
Free of other bias?	Yes	No other potential bias was found.

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

Study	Reason for exclusion
Benoldi 1991	It is a RCT, but the control group was treated with carbamazepine.
Chang 2004	PHN was defined as pain persisting at the site of shingles two weeks after the onset of acute rash.
Cui 2002	Confirmed not truly randomised by contacting the original author.
Guo 2001	The routine treatments were mismatched between two groups.
Hao 2002	Confirmed not truly randomised by contact with original author.
Huang 2004	Confirmed not truly randomised by contacting original author.
Jiang 2005	The routine treatments were mismatched between two groups.
Jiang 2008	Confirmed not a true RCT, and the duration of herpes zoster was not specified.
Keczkes 1980	The control group was treated with carbamazepine.
Li 2000	Confirmed not a true RCT.
Li 2002	Confirmed not truly randomised by contact with original author.
Liao 2005	PHN was defined as pain persisting one week after total decrustation.
Lin 2005	Confirmed not truly randomised by contact with original author.
Liu 2003	PHN was defined as pain persisting at the site of shingles two weeks after the onset of acute rash.

(*Continued*)

Liu 2005	PHN was defined as pain persisting at the site of shingles two weeks after the onset of acute rash.
Ma 2000	Confirmed not a true RCT.
Ma 2002	Confirmed not truly randomised by contacting original author.
Shi 2008	Confirmed not a true RCT.
Song 2009	Confirmed not a true RCT.
Tang 2004	Confirmed not truly randomised by contacting original author.
Yang 2000	The routine treatments were mismatched between two groups.
Yang 2002	PHN was defined as pain persisting at the site of shingles two weeks after the onset of acute rash.
Yang 2010	Confirmed not a true RCT, and PHN was not clearly defined. The duration of herpes of some patients was longer than seven days after the rash onset.
Yin 2004	The routine treatments were mismatched between two groups.
Yin 2005	The routine treatments were mismatched between two groups.
Zhang 2003	Confirmed not truly randomised by contacting original author.
Zhang 2004	The routine treatments were mismatched between two groups.
Zheng 2004	The routine treatments were mismatched between two groups.
Zhou 2000	Confirmed not truly randomised by contacting original author.
Zhou 2008	Not a true RCT.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hu 2001

Methods	A single centre, randomised controlled parallel trial.
Participants	45 patients with confirmed herpes zoster and without contraindications to glucocorticosteroids were enrolled. They were randomly assigned to the acyclovir plus dexamethasone group (20 patients) or the acyclovir alone group (25 patients).
Interventions	In the acyclovir plus dexamethasone group, patients were given 0.25 g acyclovir intravenously every 8 hours for a total of 10 days, and 5 mg dexamethasone intravenously daily. In the controlled group, only acyclovir was administered in the same way as with the other group.

Hu 2001 (*Continued*)

Outcomes	Time to cessation of new herpes eruption, time to crusting, and the presence of PHN at one month after the rash onset.
Notes	The exact course of disease from onset of herpes zoster to receipt of treatment was not specified. We tried to contact the author, but have not yet received a reply.

Lin 2002

Methods	Single centre, randomised controlled parallel design.
Participants	68 patients aged from 16 to 80 years old were enrolled and randomly assigned to the acyclovir plus prednisone group or the acyclovir alone group (34 patients in each group).
Interventions	One 200 mg-acyclovir tablet was given orally every 5 hours for 10 days, and oral prednisone (10 mg) was administered three times a day for three days. The controlled group only took acyclovir in the above specified way.
Outcomes	Time to cessation of new herpes eruption, time to cessation of pain, time to crusting, time to total healing and the presence of PHN at one month after the rash onset.
Notes	The course of herpes zoster at enrolment was one to nine days. We tried to contact the authors to get further details of patients with a disease course of less than 7 days, but we have not received a reply.

Wang 2004

Methods	A single centre, randomised controlled trial conducted in the outpatient department.
Participants	A total of 99 herpes zoster patients aged more than 40 years old were included. Inclusion criteria based on clinical manifestation was clear but exclusion criteria was not specified. Participants were randomly assigned to combined treatment group (52 cases) and controlled group (47 cases). Demographic characteristics were equal between groups; disease course was 1 to 12 days (5.5 days in average) in treatment group and 2 to 11 days (2 to11 days) in the other group.
Interventions	The combined treatment group received 0.3 g of valaciclovir orally twice per day for 7 days and 10 mg of prednisone 3 times per day for 3 days; while the comparison group received the same antiviral agent but not prednisone.
Outcomes	Numbers of patients with different degrees of relief and the presence of PHN at one month after the rash onset.
Notes	The course of herpes zoster at enrolment was 1 to12 days. We tried to contact the authors to get further details of patients with a disease course of less than 7 days, but we have not received a reply.

Xu 1999

Methods	Single centre, randomised controlled parallel design.
Participants	80 patients with confirmed herpes zoster were allocated to three treatment groups using computer-generated random numbers. Demographic characteristics, disease course and severity were equal between groups.
Interventions	The combined group (30 patients) received 4000 mg acyclovir and 40 mg prednisone orally daily for one week and then prednisone was gradually reduced; the large-dose group (25 patients) received 4000 mg oral acyclovir daily for one week; and the regular-dose group (25 patients) received 1000 mg acyclovir orally daily for one week.
Outcomes	Time to cessation of new herpes eruption, time to decrustation, time to cessation of pain and the presence of PHN were recorded and compared between groups.
Notes	The course of herpes zoster at enrolment was 1 to 15 days and the definition of PHN was not clearly specified, so we tried to contact the authors to get further details, but we have not received a reply.

Zhang 2005

Methods	A single centre, randomised controlled trial conducted in the outpatient department.
Participants	A total of 60 patients with typical herpes zoster were included, and then were randomly allocated to two groups. Patients with serious hepatic or renal insufficiency, pregnant women and women of childbearing potential, and patients with a history of hypersensitivity to acyclovir were excluded. Age, sex, disease course, clinical manifestation and severity were not significantly different between groups.
Interventions	The combined treatment group received 200 mg acyclovir orally five times per day for 10 days and 10 mg prednisone three times per day for three days; the control group only received 200 mg oral acyclovir five times per day for 10 days.
Outcomes	Time to cessation of new herpes eruption, time to cessation of pain, time to crusting, time to total healing and the presence of PHN at one month after the rash onset were all recorded.
Notes	The course of herpes zoster at enrolment was 1 to 10 days, so we tried to contact the authors to get further details, but we have not received a reply.

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The presence of PHN six months after the onset of the acute herpetic rash	2	114	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.45, 1.99]
2 The main effect of prednisone compared with no prednisone on six months evaluation of pain (generic inverse variance)	1		RR Ratios (Fixed, 95% CI)	Totals not selected
3 Serious adverse events	5	755	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.51, 5.29]
4 Non-serious adverse events	5	755	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.90, 1.87]

Comparison 2. Sub-group analysis

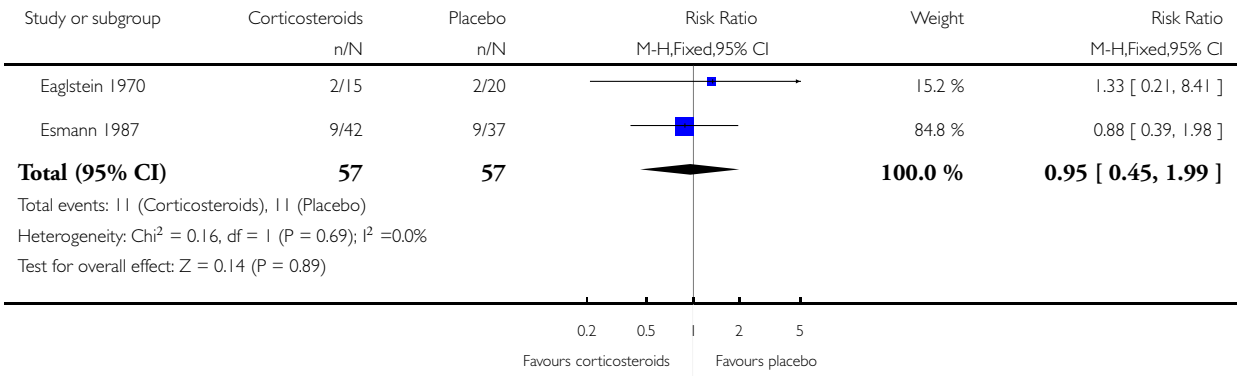
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The presence of PHN six months after the onset of the acute herpetic rash	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults aged 50 years or more	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.47, 2.04]
1.2 Adults 49 years of age or less	1	6	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 The presence of PHN six months after the onset of the acute herpetic rash.

Review: Corticosteroids for preventing postherpetic neuralgia

Comparison: 1 Corticosteroids versus placebo

Outcome: 1 The presence of PHN six months after the onset of the acute herpetic rash

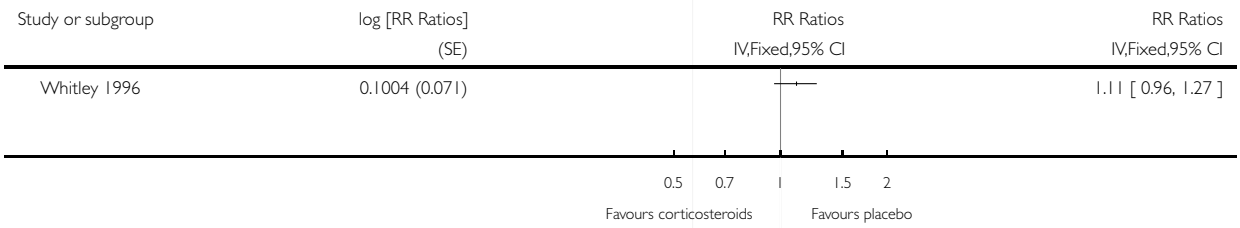


Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 The main effect of prednisone compared with no prednisone on six months evaluation of pain (generic inverse variance).

Review: Corticosteroids for preventing postherpetic neuralgia

Comparison: 1 Corticosteroids versus placebo

Outcome: 2 The main effect of prednisone compared with no prednisone on six months evaluation of pain (generic inverse variance)



Analysis 1.3. Comparison 1 Corticosteroids versus placebo, Outcome 3 Serious adverse events.

Review: Corticosteroids for preventing postherpetic neuralgia

Comparison: 1 Corticosteroids versus placebo

Outcome: 3 Serious adverse events

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Clemmensen 1984	0/20	0/20		0.0 [0.0, 0.0]
Eaglstein 1970	0/15	0/20		0.0 [0.0, 0.0]
Esmann 1987	1/42	0/37		2.65 [0.11, 63.16]
Whitley 1996	0/50	1/52		0.35 [0.01, 8.31]
Whitley 1996	1/51	0/48		2.83 [0.12, 67.76]
Wood 1994a	4/198	2/202		2.04 [0.38, 11.01]
Total (95% CI)	**376**	**379**		**1.65 [0.51, 5.29]**

Total events: 6 (Corticosteroids), 3 (Placebo)

Heterogeneity: Chi^2 = 1.18, df = 3 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 0.84 (P = 0.40)

Analysis 1.4. Comparison 1 Corticosteroids versus placebo, Outcome 4 Non-serious adverse events.

Review: Corticosteroids for preventing postherpetic neuralgia

Comparison: 1 Corticosteroids versus placebo

Outcome: 4 Non-serious adverse events

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Clemmensen 1984	1/20	0/20		3.00 [0.13, 69.52]
Eaglstein 1970	0/15	1/20		0.44 [0.02, 10.05]
Esmann 1987	0/42	0/37		0.0 [0.0, 0.0]
Whitley 1996	9/50	10/52		0.94 [0.42, 2.11]
Whitley 1996	7/51	6/48		1.10 [0.40, 3.04]
Wood 1994a	38/198	26/202		1.49 [0.94, 2.36]
Total (95% CI)	**376**	**379**		**1.30 [0.90, 1.87]**

Total events: 55 (Corticosteroids), 43 (Placebo)

Heterogeneity: Chi^2 = 1.81, df = 4 (P = 0.77); I^2 =0.0%

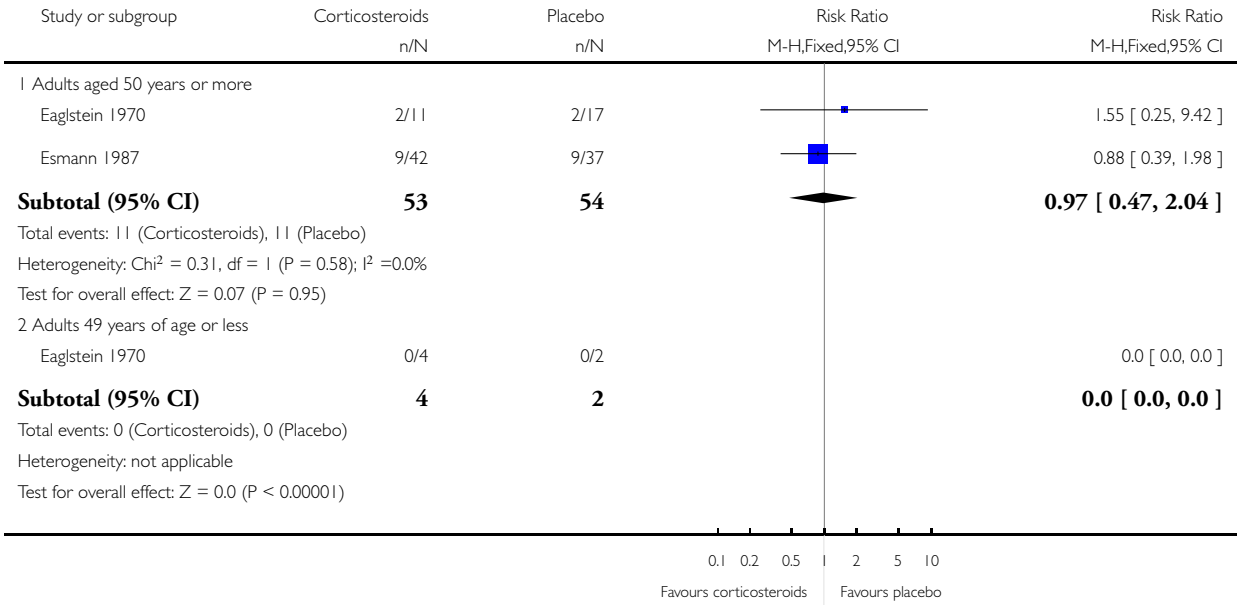
Test for overall effect: Z = 1.40 (P = 0.16)

Analysis 2.1. Comparison 2 Sub-group analysis, Outcome 1 The presence of PHN six months after the onset of the acute herpetic rash.

Review: Corticosteroids for preventing postherpetic neuralgia

Comparison: 2 Sub-group analysis

Outcome: 1 The presence of PHN six months after the onset of the acute herpetic rash



APPENDICES

Appendix 1. Ovid MEDLINE Search Strategy

1. exp Herpes Zoster/
2. herpes zoster.mp.
3. shingle$.mp.
4. neuralgia/
5. (postherpetic or post herpetic).mp.
6. 4 and 5
7. PHN.tw.
8. postherpetic neuralgia.mp.
9. post herpetic neuralgia.mp.
10. post-herpetic neuralgia.mp.
11. or/1-3,6-10

12. Glucocorticoids/
13. glucocorticoid$.mp.
14. adrenal cortex hormone/
15. adrenal cortex hormone$.mp.
16. corticosteroid$.mp.
17. exp Steroids/
18. steroid$.mp.
19. Prednisolone/
20. prednisolone$.mp.
21. TRIAMCINOLONE/
22. triamcinalone$.mp.
23. DEXAMETHASONE/
24. dexamethasone$.mp.
25. triamcinolone$.mp.
26. HYDROCORTISONE/
27. hydrocortisone$.mp.
28. PREDNISONE/
29. prednisone$.mp.
30. or/12-29
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized controlled trials/
34. random allocation/
35. double-blind method/
36. single-blind method/
37. or/31-36
38. animals/ not humans/
39. 37 not 38
40. clinical trial.pt.
41. exp clinical trial/
42. (clin$ adj25 trial$).ti,ab.
43. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab.
44. placebos/
45. placebo$.ti,ab.
46. random$.ti,ab.
47. research design/
48. or/40-47
49. 48 not 38
50. 49 not 39
51. comparative study/
52. exp evaluation studies/
53. follow up studies/
54. prospective studies/
55. (control$ or prospectiv$ or volunteer$).ti,ab.
56. or/51-55
57. 56 not 38
58. 57 not (39 or 50)
59. 39 or 50 or 58
60. 11 and 30 and 59

61 60 and 20060901:20100204.(ed).
62 randomized controlled trial.pt.
63 controlled clinical trial.pt.
64 randomized.ab.
65 placebo.ab.
66 drug therapy.fs.
67 randomly.ab.
68 trial.ab.
69 groups.ab.
70 or/62-69
71 (animals not (animals and humans)).sh.
72 70 not 71
73 11 and 30 and 72
74 73 not 60
75 73 and 61
76 74 or 75

Appendix 2. Ovid EMBASE Search Strategy

1. Randomized Controlled Trial/
2. Clinical Trial/
3. Multicenter Study/
4. Controlled Study/
5. Crossover Procedure/
6. Double Blind Procedure/
7. Single Blind Procedure/
8. exp RANDOMIZATION/
9. Major Clinical Study/
10. PLACEBO/
11. Meta Analysis/
12. phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
13. (clin$ adj25 trial$).tw.
14. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
15. placebo$.tw.
16. random$.tw.
17. control$.tw.
18. (meta?analys$ or systematic review$).tw.
19. (cross?over or factorial or sham? or dummy).tw.
20. ABAB design$.tw.
21. or/1-20
22. human/
23. nonhuman/
24. 22 or 23
25. 21 not 24
26. 21 and 22
27. 25 or 26
28. exp *Herpes Zoster/
29. herpes zoster.tw.
30. shingle$.tw.
31. neuralgia/
32. (postherpetic or post herpetic).tw.
33. 31 and 32
34. PHN.tw.
35. postherpetic neuralgia.tw.
36. post herpetic neuralgia.tw.
37. post-herpetic neuralgia.tw.
38. or/28-30,33-37
39. Glucocorticoid/
40. glucocorticoid$.tw.
41. adrenal cortex hormone/
42. adrenal cortex hormone$.tw.
43. corticosteroid$.tw.
44. exp Steroid/
45. steroid$.mp.
46. Prednisolone/
47. prednisolone$.tw.
48. TRIAMCINOLONE/
49. triamcinalone$.tw.
50. DEXAMETHASONE/

51. dexamethasone$.tw.
52. triamcinolone$.tw.
53. HYDROCORTISONE/
54. hydrocortisone$.tw.
55. PREDNISONE/
56. prednisone$.tw.
57. or/39-56
58. 27 and 38 and 57
59 limit 58 to em=200646-201004
60 crossover-procedure/
61 double-blind procedure/
62 randomised controlled trial/
63 single-blind procedure/
64 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
65 or/60-64
66 human/
67 65 and 66
68 nonhuman/ or human/
69 65 not 68
70 67 or 69
71 27 and 38 and 70
72 71 not 58
73 71 and 59
74 72 or 73

Appendix 3. Cochrane Library CENTRAL Search Strategy

#1 MeSH descriptor Herpes Zoster explode all trees
#2 "herpes zoster"
#3 shingle*
#4 MeSH descriptor Neuralgia, Postherpetic, this term only
#5 PHN
#6 (postherpetic or post herpetic or post-herpetic) and neuralgia
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 MeSH descriptor Glucocorticoids explode all trees
#9 glucocorticoid*
#10 MeSH descriptor Adrenal Cortex Hormones explode all trees
#11 adrenal cortex hormone*
#12 corticosteroid*
#13 MeSH descriptor Steroids explode all trees
#14 steroid*
#15 MeSH descriptor Prednisolone explode all trees
#16 prednisolone*
#17 MeSH descriptor Triamcinolone explode all trees
#18 triamcinalone*
#19 MeSH descriptor Dexamethasone explode all trees
#20 dexamethasone*
#21 triamcinolone*

#22 MeSH descriptor Hydrocortisone explode all trees
#23 hydrocortisone*
#24 MeSH descriptor Prednisone explode all trees
#25 prednisone*
#26 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 #7 and #26

Appendix 4. LILACS Search Strategy

(Mh Herpes Zoster OR Tw herpes zoster OR Tw shingle$ OR (Mh neuralgia AND (postherpetic OR post herpetic)) OR Tw PHN OR Tw postherpetic neuralgia OR Tw post herpetic neuralgia OR post-herpetic neuralgia) AND (Mh Glucocorticoids OR Tw glucocorticoid$ OR Mh adrenal cortex hormone OR Tw adrenal cortex hormone$ OR Tw corticosteroid$ OR Mh Steroids OR Tw steroid$ OR Mh Prednisolone OR Tw prednisolone$ OR Mh TRIAMCINOLONE OR Tw triamcinalone$ OR Mh DEXAMETHASONE Or Tw dexamethasone$ OR Tw triamcinolone$ OR Mh HYDROCORTISONE OR Tw hydrocortisone$ OR Mh PREDNISONE OR Tw prednisone$)
AND ((Pt randomised controlled trial OR Pt controlled clinical trial OR Mh randomised controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))

Appendix 5. Chinese Biomedical Retrieval System Database search strategy

(NB. all of the search terms were translated to Chinese terms when we conducted the searches)
1. herpes zoster
2. postherpetic neuralgia
3. PHN
4. shingle
5. 1-4/or
6. herpes
7. neuralgia
8. 6 and 7
9. 5 or 8
10.corticorsteroid
11.hormone
12.steroid
13.prednisone
14.prednisolone
15.triamcinolone
16.dexamethasone
17.hydrocortisone
18.10-17/or
19.random
20.control
21.clinical trial
22.blind procedure
23.placebo
24.19-23/or

25.9 and 18 and 24

WHAT'S NEW

Last assessed as up-to-date: 3 February 2010.

Date	Event	Description
8 November 2010	New citation required but conclusions have not changed	New authors have joined the review update team
17 July 2010	New search has been performed	For the 2010 update we updated the searches, but found no new trials. We assessed risk of bias using the new methods, added a 'Summary of findings' table and revised the review.

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 1, 2008

Date	Event	Description
14 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ning Chen and Mi Yang performed the updated searches, identified the studies, assessed their methodological quality according to new criteria, extracted the data, and produced the draft of the updated review. Li He is a consultant and expert in this field. She is the contact author and originally suggested the review and contributed to writing the final version of the protocol and review. She also contributed to updating the review and offering expert advice. Dongping Zhang developed and wrote the protocol and first review, and entered the text into Review Manager. Muke Zhou contributed to developing and writing the final version of the protocol and review. Cairong Zhu contributed to writing the section of the manuscript that refers to the planned statistical analysis.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this 2010 update we assessed risk of bias using new methods, and added a 'Summary of findings' table. The protocol was changed to exclude quasi-RCTs, because RCTs are thought to be the only way to prevent systematic differences of baseline characteristics between intervention groups, according to the latest Corchrane Handbook. However, no quasi-RCTs were found.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Neuralgia, Postherpetic [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans