

Oral Corticosteroid Therapy for Preventing Postherpetic Neuralgia: A Systematic Review and Meta-analysis

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Abstract The purpose of this systematic review was to examine the efficacy of oral corticosteroids for prevention of postherpetic neuralgia (PHN). Randomized controlled trials of patients suffering from herpes zoster comparing corticosteroids to control therapy (placebo or carbamazepine) or acyclovir were included. Three electronic databases (MEDLINE via PubMed, Web of Science and The Cochrane Library) were searched. Two authors assessed all eligible studies for risk of bias. Ninety-one references were found. After applying inclusion/exclusion criteria 7 studies were eligible for this systematic review. All 7 studies were at high risk of bias. Corticosteroids, rather than carbamazepine, protected the patients against PHN (Relative Risk [RR] = 0.543, 95% CI 0.087 to 3.376, $p=0.512$), however the results were not statistically significant. Additionally, a second meta-analysis showed that the use of corticosteroids does not prevent PHN compared to the use of a placebo (RR=0.990, 95% CI 0.092 to 10.663, $p=0.994$). Mild and reversible side effects were reported in patients taking only corticosteroids; two serious cardiovascular events were reported in the patients prescribed acyclovir and corticosteroid, though those two events were probably unrelated to the therapy. Individual studies reported quality of life improvements and reduction in the incidence and severity of pain with the addition of prednisone to acyclovir therapy; however the heterogeneity of the outcomes and comparison group prevented from performing meta-analyses on these outcomes. Due to the low number of studies, high risk of bias, heterogeneity of the outcomes and comparison groups, the evidence this systematic review provided was of low quality.

Keywords Postherpetic Neuralgia (PHN), Corticosteroids, Placebo, Herpes Zoster, and Randomized Controlled Trials

1. Introduction

Varicella zoster, the virus that causes the childhood

Varicella (chickenpox), never leaves the body once it has been introduced. Once chickenpox has resolved, the virus retreats into the dorsal root ganglia where it remains dormant. In most cases, it remains inactive for a lifetime, however, the virus can become active again if the host's immunity is weakened by disease, stress or aging. If the virus is reactivated, it causes a painful cutaneous rash known as shingles or herpes zoster. Early symptoms of shingles include pain, burning, tingling and numbness in the area around the affected nerves several days before the rash appears. These symptoms may be followed by headache, light sensitivity and flulike symptoms (usually without fever) just before or along with the start of a rash that usually lasts three to five weeks [1, 2]. The rash starts with blistering, followed by crusting over and finally healing [1]. After resolution of the lesions associated with herpes zoster, persistent pain may continue and can profoundly affect a patient's quality of life [3, 4]. Pain may continue for months or years or a lifetime and it is commonly diagnosed as postherpetic neuralgia (PHN). This chronic pain is the most common complication of herpes zoster and its prevalence increases with age. An estimated 12.5% of patients with herpes zoster aged 50 years or older developed PHN three months after zoster onset [5].

Postherpetic pain may take several forms including allodynia in which a stimulus such as light touching is perceived as painful, hyperpathia in which severe pain induced by nociceptive stimuli is reported by the patient and dysesthesia where sensations are felt when there are no stimuli present [6, 7]. Due to PHN complexity, management is difficult. A variety of treatments are offered but their effectiveness in reducing symptoms is ambiguous. Corticosteroids are used as anti-inflammatory therapy for patients suffering with pain and inflammation during acute herpes zoster outbreak for prevention of PHN [6]. Previous studies, aimed at assessing the effectiveness of corticosteroid therapies (prednisone or triamcinolone) in preventing PHN, provide contradictory results [8, 9]. In their review, Han et al. [10] concluded that oral corticosteroids did not prevent PHN six months after herpes onset. The changes or symptoms that

occur during PHN are complicated, therefore, the efficacy of a single therapy treatment for controlling PHN is uncertain [11]. Three trials compared an antiviral agent (acyclovir) alone with a combination of oral corticosteroids and acyclovir, however, the effectiveness of these combination therapies was inconclusive [12–14]. Despite the absence of evidence regarding interventions with corticosteroids, these therapies are commonly used in the treatment of herpes zoster. Therefore, a systematic review to examine the effectiveness of oral corticosteroids in preventing and treating PHN is needed. This work addresses the question of whether intervention therapies such as oral corticosteroid therapy can prevent or reduce PHN in patients with herpes zoster.

2. Materials and Methods

The following electronic databases were searched on June 7, 2016: MEDLINE via PubMed, the Web of Science and The Cochrane Library. The search strategy was as follows: (Postherpetic neuralgia OR post herpetic neuralgia) AND (Corticosteroid OR Prednisone). PubMed search was limited to English language and Human species. An update of the search on April 24th, 2017 did not produce any new relevant studies for inclusion. Studies were selected using the following criteria: 1) limited to randomized controlled trials in the prevention of PHN, 2) participant patients were limited to those with painful herpes zoster in the first week (0-7 days) of vesicles formation before study enrollment, 3) corticosteroids (prednisone, prednisolone or triamcinolone) administered orally with or without acyclovir and 4) trials comparing effectiveness of corticosteroids with control treatment (placebo or carbamazepine) or acyclovir.

Editorials, letters to the editor, commentaries, reviews, case studies, animal studies, cost-effectiveness studies, pharmacokinetic studies and guidelines were omitted. Based on the inclusion criteria, two reviewers (AH, MA) independently screened all abstracts and titles resulting from the electronic search as well as the cross-referencing process, and decided to include or exclude the reference for full-text review. For those references where the inclusion was unclear, the full article was assessed for inclusion/exclusion criteria. Reasons for exclusion were recorded in a table format for

further reference.

Two independent reviewers (AH, MA) were responsible for extracting the data from the eligible studies related to participant's demographics, interventions, control therapy and outcomes. The assessment of risk of bias with respect to the Randomized Controlled Trials was initially implemented independently by two authors (MA, AH) in accordance with the method described in the Cochrane Handbook for Systematic Reviews of Interventions [15]. (Table 1) The extraction data table prepared for each study included: *primary outcome*, in this systematic review was the incidence of PHN, defined as pain lasting more than thirty days after onset of herpes zoster; *secondary outcomes*, reported by some of the studies included in this systematic review: 1) Pain intensity; the intensity of pain in the acute phase among the treated and control group (absent, slight, moderate or severe). 2) Rate of healing; the last day with new lesions, the first day without new vesicles, the first day with full crusting, the time to 100 % healing of the rash, the times of first cessation of pain and the complete cessation of pain. 3) Quality of life parameters; return to 100% usual activities, return to uninterrupted sleep, and cessation of analgesic agents during a 6-month period. 4) Adverse events reported in the study; serious adverse events were counted as those events which were life threatening requiring prolonged hospitalization or caused death of the patient.

Studies reporting the number of patients developing PHN during the trial were included in the meta-analysis. Risk ratios with 95% Confidence Intervals (CI) were reported for each eligible study in the meta-analysis as well as the overall pooled result. Statistical heterogeneity was assessed by means of the Cochran's test [16] and quantified by the I^2 statistic [17]. To measure the treatment effects, the estimates of the effect were combined using a random-effects model if statistically significant heterogeneity was found (Cochran's Q test $p < .010$), otherwise, the fixed-effect model was used. Subgroup analyses are presented for studies comparing corticosteroids versus a placebo group and corticosteroids versus carbamazepine, used as a control therapy in two studies. All statistical analyses were performed with Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ, USA). Quality of evidence assessment was conducted using the software GRADE profiler[®] [15].

Table 1. Summary of risk of bias for eligible studies.

Study	Random Seq. Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Benoldi et al. [18] (1991)	???	+++	+++	----	----	+++	+++
Clemmensen and Andersen, [19] (1984)	???	???	???	----	----	+++	+++
Eaglstein et al. [8] (1970)	???	----	----	----	----	+++	+++
Esmann et al. [13] (1987)	???	???	???	----	----	+++	+++
Keczkes and Basheer [9] (1980)	???	+++	+++	----	----	+++	+++
Whitley et al. [14] (1996)	----	----	----	----	----	+++	+++
Wood et al. [12] (1994)	----	???	???	----	----	+++	+++

KEY: +++ High risk of bias; ---- Low risk of bias; ??? Unclear risk of bias

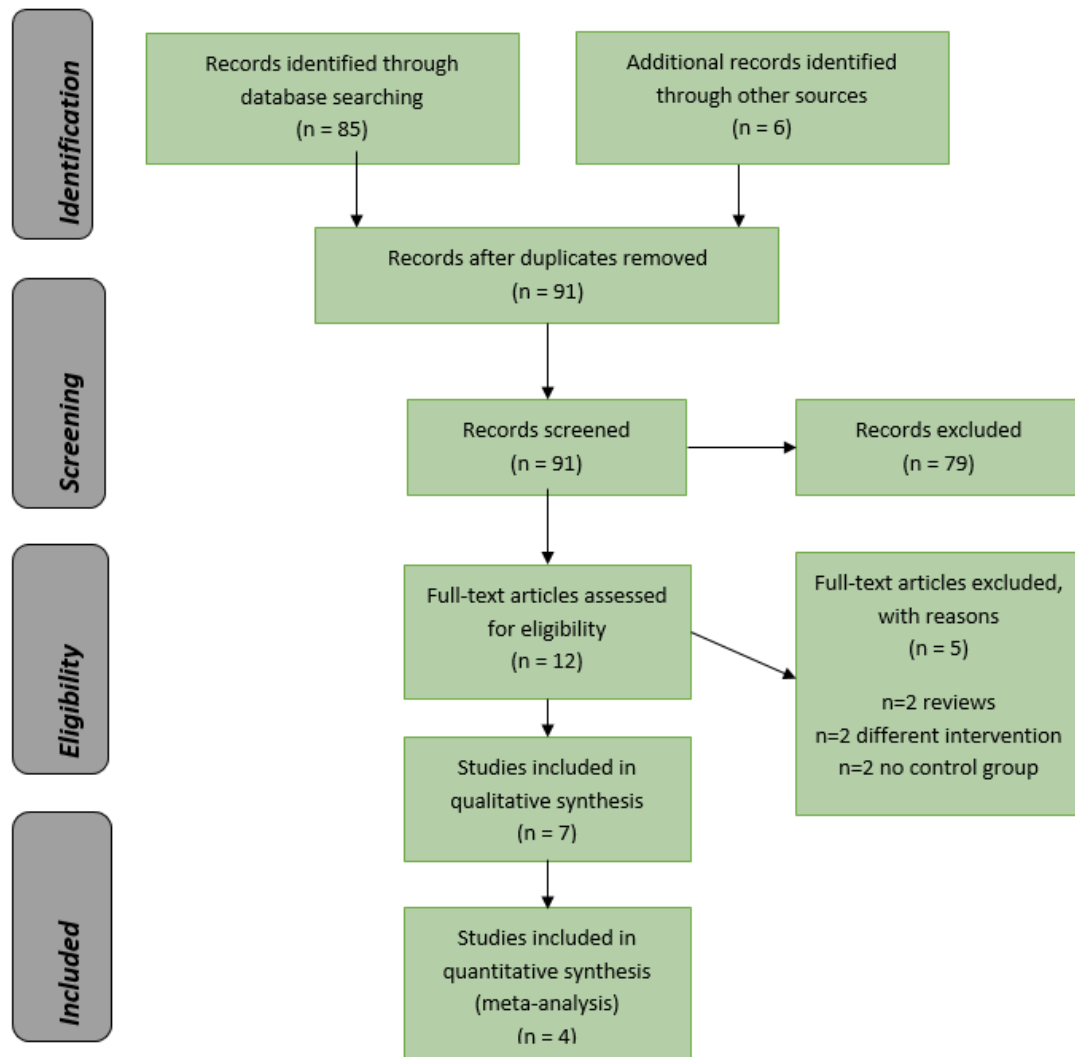


Figure 1. PRISMA Flow Diagram

3. Results

The initial search strategy yielded 85 unduplicated references and 6 additional references were found during cross-referencing citations of the reviews and included papers, which based on the abstracts they were reduced to 12 relevant manuscripts. Main reasons for exclusion were: abstract of some conference proceedings without details for inclusion in this review ($n=1$), case report/case series ($n=3$), different conditions ($n=47$), different interventions ($n=9$), different outcome reported than incidence or severity of PHN ($n=1$), not an RCT ($n=1$), no placebo group ($n=1$), opinion/editorial ($n=3$) or a review ($n=13$). All twelve manuscripts identified were further analyzed for inclusion independently by two review authors and five more studies were rejected after full-text review. Figure. 1 shows the PRISMA flow diagram.

The seven included studies were RCTs, 67% of the studies

were double-blinded, while the remaining [9, 18] had no indication of whether or not they were double blinded (Table 2). The sample size ranged from 35 [8] to 349 [12] participants. All participants were diagnosed with early signs of herpes zoster, all were adults ranging in age from 21 to 91 years old. The gender of the participants was provided in all of the studies except for one [14] in which the study outlined that slightly more than 50% of the participants were women. The two corticosteroids under study were prednisone and triamcinolone; three studies compared corticosteroid to a placebo [8, 13, 19], two compared corticosteroid to carbamazepine [9, 18] and two compared acyclovir with or without a concomitant corticosteroid [12,14] for the treatment of herpes zoster and prevention of PHN. Drug dosage for each intervention is indicated in Table 5.

The risk of bias of all 7 studies are shown in Table 1 and summarized in Figure 2. Overall, the risk of bias for all studies was high.

Table 2. Summary of eligible studies

Reference	Year, Country, Sample Size	Participants Gender (F/M) Mean age (years)	Follow-up	Interventions and sample size	Inclusions	Bias
Benoldi et al.[18] (1991)	1991, USA, N=36	20F/16M Mean age: 65.8	1 year	Prednisone (n=9) Acyclovir (n=9) Radiotherapy (n=9) Carbamazepine (n=9)	Over 50 years of age, with early (less than 72 hours), severe, painful HZ	High
Clemmensen and Andersen, [19] (1984)	1984, Denmark N=55	1)Prednisone 6F/13M Mean age: 56 2) ACTH 7F/10M Mean age: 55 3) Placebo 9F/10M Mean age: 56	6 weeks	Prednisone (n=19) ACTH (n=17) Placebo (n=19)	Early symptoms of HZ (3.8- 4.1 days after the onset of symptoms.)	High
Eaglstein et al. [8] (1970)	1970 USA, N= 34	Age: 21-91 years old	8 weeks	Triamcinolone (n=15) Placebo (Lactose tablet) (n=19)	Adults with maximum 5 days after the onset of skin lesions.	High
Esmann et al. [13] (1987)	1987 Denmark N=78	1)Acyclovir+prednisolone 24F/17M Mean Age: 72.8 2) Acyclovir+ placebo 29F/8M Mean Age: 71.4	26 weeks	Acyclovir+prednisolone (n=41) Acyclovir+placebo (n=37)	60 years old patients, the rash and /or the pain had been present for less than 96h before admission.	High
Keczkes and Basheer [9] (1980)	1980 England, N=40	1) Prednisolone 6F/14M Mean Age: 66.4 2) Carbamazepine 6F/14M Mean Age: 68.5	Over 1 year	Prednisolone (n=20) Carbamazepine (n=20)	Patients over 50 years of age with early, severe painful herpes zoster	High
Whitley et al.[14] (1996)	1996 USA N=201	1) Acyclovir+prednisone 27F/24M Age: 63 2) Acyclovir 27F/21M Age: 62 3) Prednisone 24F/26M Age: 60 4) Placebo 27F/25M Age: 61	6 months	Acyclovir+prednisone (n=51) Acyclovir (n=48) Prednisone (n=50) Placebo group (n=52)	Patients older than 50 years of age who had localized herpes zoster that developed less than 72 hours before study enrollment.	High
Wood et al. [12] (1994)	1994, England N=400	1) 7-day acyclovir + 21-days steroid 62F/37M Mean Age: 59 2) 7-day acyclovir 62F/39M Mean age: 58 3) 21-day acyclovir + 21- days steroid 60F/39M Mean Age: 60 4) 21-day acyclovir 63F/38M Mean Age: 59	6 months	7-day acyclovir with 21-day Prednisolone (n=99) 7-day acyclovir (n=101) 21-day acyclovir with 21-day Prednisolone (n=99) 21-day Acyclovir (n=101)	Adults >18 years of age without immune dysfunction due to cancer or immunosuppressive therapy, who presented with a clinical diagnosis of herpes zoster as and had a rash for 72 hours or less and at least moderate pain.	High

ACTH=Adrenocorticotrophic hormone.

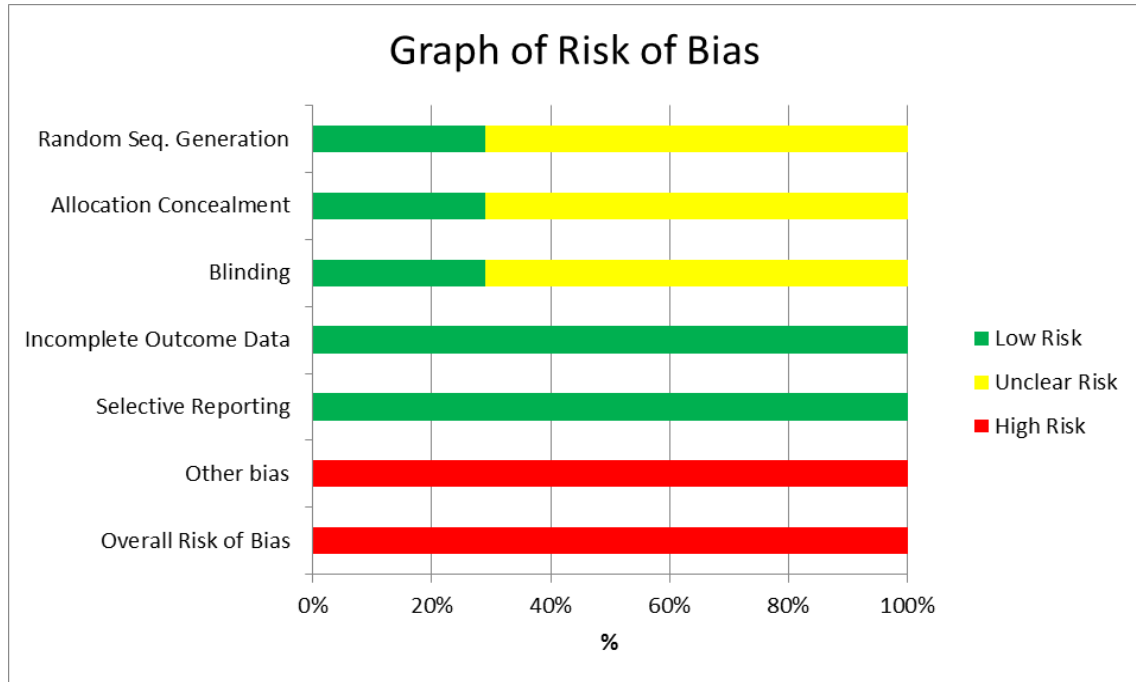
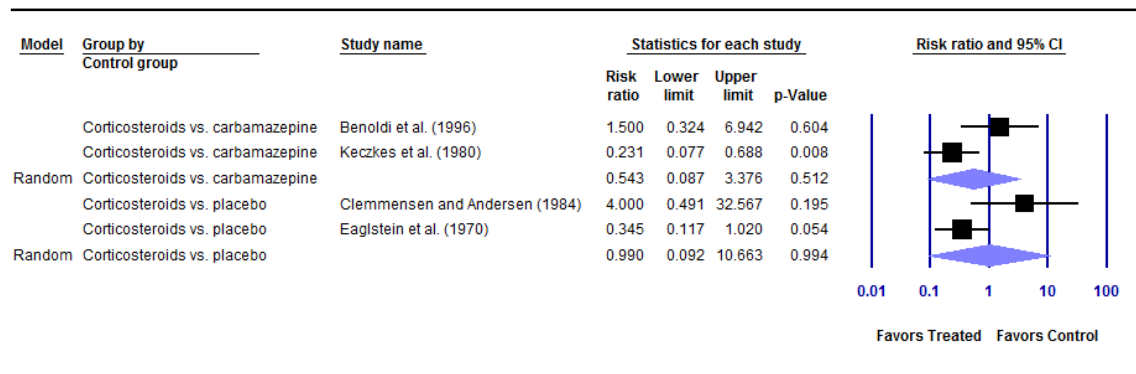


Figure 2. Graph of risk of bias for eligible studies.

Table 3. Summary of outcomes for incidence of PHN in RCTs comparing corticosteroids to carbamazepine

Study	Interventions	Outcome	Incidence of PHN in Corticosteroid group (%)	Incidence of PHN in Control group (%)	RR [95% CI] p-value
Benoldi et al. [18] (1996)	Prednisone 35mg/day for 10 days with gradual reduction to zero over the next 3weeks (n=9) Carbamazepine 100 mg four times a day for 4 weeks (n=9)	Incidence of PHN measured at 2 months	3/9 (33%)	2/9 (22%)	RR=1.5 [0.324,6.942] P=0.604
Keczkes and Basheer[9] (1980)	Prednisolone 40 mg daily for 10 days with gradual reduction over a period of 3 weeks (n=20) Carbamazepine 100 mg four times daily for 4 weeks (n=20)	Incidence of PHN measured at 2 months	3/20 (15%)	13/20 (65%)	RR=0.231 [0.077,0.688] P=0.008

Incidence of PHN: treated versus controls



Random effects model

Figure 3. Subgroup analysis by control group: Corticosteroids versus carbamazepine or placebo.

3.1. Effects of Interventions

Of the seven studies included in the qualitative synthesis, five [8, 9, 13, 18, 19] reported incidence of PHN and two [12, 14] did not and could not be included in the meta-analysis. Two studies compared corticosteroids versus placebo [8, 19], two compared corticosteroids versus carbamazepine [9, 18], and three studies [12–14] compared corticosteroids + acyclovir to acyclovir alone. Only studies comparing similar interventions were pooled together in a meta-analysis. Subgroup analyses comparing corticosteroids to placebo or carbamazepine are presented in Figure 3.

3.1.1. Corticosteroids vs. Carbamazepine.

Two studies reported the incidence of PHN in patients treated with corticosteroids versus carbamazepine [9, 18] (Table 3). In Benoldi et al [18], the patients started at 35mg of prednisone per day for 10 days with gradual reduction to zero over the next 3 weeks, compared to 40 mg prednisolone in Keczkas and Basheer [9]. Sample size was 9 in Benoldi et al [18] compared to 20 participants in each group in Keczkas and Basheer [9]. Both studies compared to carbamazepine 100 mg four times a day for 4 weeks. There was moderate heterogeneity among the two studies [9], [18] comparing corticosteroids with carbamazepine (Q-test $p=0.051$; $I^2 = 73\%$). Using the random-effects model, the pooled results showed that patients treated with corticosteroids were less likely to develop PHN than patients taking carbamazepine (RR=0.543, 95% CI 0.087 to 3.376, $p=0.512$) but this difference was not statistically significant (Figure 3).

In Benoldi et al [18], the intensity of pain was measured in the acute phase and it decreased in the prednisone group from severe to slight or absent ($p<0.5$) in six patients. In the control group only one patient had pain reduction from severe to moderate ($p<0.5$). In Keczkas and Basheer [9] pain relief time was measured after PHN: no patient had pain exceeding 6 months in the prednisolone group while four patients had pain lasting 1 year or longer in the carbamazepine group. They also measured the skin healing time, which was significantly shorter in the prednisolone group (3.65 weeks) compared to the

carbamazepine group (5.25 weeks). In conclusion, though PHN could not be prevented, the severity or duration of PHN was reduced more in the prednisolone group than in the carbamazepine group.

3.1.2. Corticosteroids vs. Placebo

Two studies compared corticosteroids versus placebo and were included in a meta-analysis [8, 19] (Table 4; Figure 3). Two different corticosteroids were used in the studies: in the first study [19], patients received 45mg of prednisone daily during the first week, 30mg daily in the second week and tapering to zero during the third week, compared to 48mg/day of triamcinolone for 7 days, 24mg/day for 7 days and 16mg/day for 7 days (a total of 3 weeks) in the second study⁸. The first study measured the incidence of PHN at 6 weeks [19] and the second one at 8 weeks. Sample sizes were similar in both studies. There was statistically significant heterogeneity among the two studies [8, 19] comparing corticosteroids with placebo (Q-test $p=0.042$; $I^2 = 76\%$) (Table 4). Using the random-effects model, the pooled results showed that corticosteroids did not significantly prevent PHN compared to placebo (RR=0.990, 95% CI 0.092 to 10.663, $p=0.994$) (Figure 3).

Whitley et al [14] showed that healing was not accelerated in patients receiving prednisone + acyclovir placebo as compared with patients receiving two placebos. However, in terms of quality of life, prednisone recipients were 1.74 times ($p<0.05$) more likely to return to 100% usual activity than were patients who did not receive prednisone [14], in conclusion, though healing was not improved in the corticosteroids group, quality of life was improved. Clemmensen and Andersen [19] reported no significant differences between the prednisone group and the placebo group in degree of pain, number of days until no further vesicles appeared or until all disappeared, or until crusts appeared. Eaglstein et al [8] did not report significant differences in skin healing time between corticosteroids and placebo groups [8]. Some patients in this study received analgesics of morphine class if needed [19]. That could have potentially biased the results if patients in the placebo group had less pain due to the co-intervention.

Table 4. Summary of outcomes for incidence of PHN in RCTs comparing corticosteroids to placebo

Study	Interventions	Outcome	Incidence of PHN in Corticosteroid group (%)	Incidence of PHN in Placebo group (%)	RR [95% CI] p-value
Clemmensen and Andersen, [19] (1984)	Prednisone 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 (n=19)	Incidence of PHN at 6 weeks	4/19 (21%)	1/19 (5.3%)	RR=4.0 [0.491,32.6] p=0.195
	Placebo (n=19)				
Eaglstein et al. [8] (1970)	Triamcinolone 48 mg/day for seven days, 24 mg/day for seven days, and 16 mg/day for seven days. (n=15)	Incidence of PHN at 8 weeks	3/15 (20%)	11/19 (73%)	RR=0.345 [0.117,1.020] p=0.054
	Placebo (n=19)				

3.1.3. Corticosteroid vs. Acyclovir

One study provided incidence data of PHN in a group treated with corticosteroid compared to a group treated with acyclovir at two months (33% in corticosteroids group versus 22% in acyclovir group; $p > .05$) [18]. At six months after the acute phase, only patients in the acyclovir group did not develop neuralgia however, one in nine patients in the prednisone group, one in nine patients in the radiotherapy group and one in nine in the carbamazepine group developed PHN. The other study comparing corticosteroids versus acyclovir [14] did not report the incidence of PHN and could not be included in the meta-analysis. The authors concluded that the resolution of PHN was not significantly accelerated in any active-treatment group (acyclovir or prednisone or acyclovir with prednisone) compared with the placebo group.

Benoldi et al. [18] measured the intensity of pain in the acute phase and reported pre- and post-treatment results; in the prednisone group, six patients had their pain reduced from severe to slight or absent ($p < 0.5$) while in the acyclovir group, five patients had their pain decreased from severe to slight or absent ($P < 0.1$). In a second study [14], patients who received prednisone, regardless of whether they also received acyclovir, were 2.28 times more likely to have resolution of acute pain during the first months after disease onset than were patients who did not receive prednisone. Also, prednisone recipients were 1.74 times more likely to return to 100% usual activity than were patients who did not receive prednisone while acyclovir recipients were 1.90 times more likely to return to 100% usual activity than were patients who did not receive acyclovir [14].

3.1.4. Acyclovir + Corticosteroids vs. Acyclovir Alone

Three studies [12–14] compared the efficacy of acyclovir + corticosteroids to acyclovir alone, however no PHN incidence was reported by treatment group and a meta-analysis could not be conducted.

Whitley et al. [14] reported no statistically significant difference ($p = .10$) in incidence of PHN between acyclovir + prednisone compared to patients taking acyclovir alone. However, patients receiving acyclovir + prednisone had statistically significant improved quality of life; accelerated time to cessation of acute neuritis ($RR = 3.02$; $p < .05$), accelerated time to return to uninterrupted sleep ($RR = 2.12$, $p < .05$), time to return to usual daily activity ($RR = 3.22$, $p < .05$) and time to cessation of analgesic therapy ($RR = 3.15$; $p < .05$). Therefore, they concluded that in relatively healthy persons older than 50 years of age who have localized herpes zoster, acyclovir + prednisone therapy can improve quality of life [14]. Wood et al. [12] reported no additional reduction of the frequency of PHN with neither steroid or acyclovir for 21 days treatment compared to 7-days. The authors suggested that the addition of prednisolone to acyclovir may confer additional benefit in the healing of rash and in the incidence and severity of pain during the first few weeks of illness but that it has no appreciable influence on the incidence or severity of PHN. In conclusion, acyclovir + corticosteroids may reduce the severity of pain and improve quality of life compared to corticosteroids alone, however no evidence was available in support of the prevention of PHN [12]

3.2. Side Effects Reported in Included Articles

As reported in Table 5, side effects were mostly mild in nature in the corticosteroids only group (increasing blood sugar, cutaneous dissemination). Only two studies [13, 14] reported side effects which were serious in nature. In Esmann et al [13] one patient in the acyclovir + prednisolone group had cardiac insufficiency and in Whitley et al [14] one patient, again from the acyclovir + prednisone group, died of myocardial infarction at day 26. It is unknown whether these two incidents were related in any way to pharmaceuticals or procedures used in the studies. In one study [12], 21% of the patients in the acyclovir + prednisolone group had side effects compared to 12% in the acyclovir only group.

Table 5. Dosage, side effects and co-interventions reported in included papers.

Study	Interventions and Dosage	Co-interventions (additional medications taken by the patients)	Side effects by Group
Benoldi et al. [18] (1991)	Prednisone 35mg/day x10days with gradual reduction to 0 over next 3 weeks (n=9) Acyclovir 800mg 5xday for 7 days (n=9) Radiotherapy 150 rad twice a week for 2 weeks (n=9) Carbamazepine 100 mg 4xday for 4 weeks (n=9)	<i>Topical treatment:</i> Meclocyline ointment No <i>analgesics</i> were allowed during the acute phase of illness.	No side effects were observed in any group
Clemmensen and Andersen,[19] (1984)	Prednisone 45mg/daily x 1 st week, 30mg/daily x 2 nd week, 15mg/daily x 3 rd week tapered to zero (n=19) ACTH 1mg IM 3 times/week to total 7 times (n=17) Placebo (n=19)	<i>Topical treatment:</i> Carbowax 1500© once daily <i>Analgesics were allowed:</i> Acetylsalicylic acid 500mg Codeine phosphate 10mg Maximum daily dose of 8 tablets Analgesics (morphine class) allowed on an emergency basis.	In <i>prednisone</i> group: (mild and reversible) Increasing blood sugar In <i>ACTH</i> group: 1. Uncomfortable dizziness 2. Moderate periorbital edema

Eaglstein et al.[8] (1970)	Triamcinolone 8mg/2 capsules 3x day x 1 week, 1 capsules 3x day x 1 week, 1 capsules 2x day x 1 week (n=15) Placebo (lactose) (n=19)	<i>Analgesics were allowed:</i> Codeine 64 mg. Tap water soaks to the skin lesions.	No side effects were reported
Esmann et al.[13] (1987)	Acyclovir 800mg/5x day x 7 days + Prednisolone 40 mg daily for 7days, 30 mg for 4 days, 20 mg for 3 days, 10 mg for 4 days, and finally 5 mg for 3 days. (n=41) Acyclovir + placebo 21 Days (n=37)	<i>Topical treatment:</i> carbowax containing 0.2% chlorhexidine and 10% lignocaine for skin lesions and 3% acyclovir ointment for eye lesions 5 times daily <i>Analgesics were allowed:</i> Authors didn't mention the name or the route of administration.	In <i>Acyclovir+Prednisolone</i> group: 1 patient had acute cardiac insufficiency (this patient was withdrawn during the first 1-2 weeks from the study start.)
Keczkes and Basheer [9] (1980)	Prednisolone 40mg/day x 10days, during 3 weeks to zero (n=20) Carbamazepine 100mg/4 x day for 4 weeks (n=20)	<i>Topical treatment:</i> Neomycin sulphate 0.25% Gramicidin 0.025% ointment Talcum powder <i>No analgesics were allowed during the acute phase of illness.</i>	No side effects were reported
Whitley et al.[14] (1996)	Acyclovir + prednisone(n=51) Acyclovir (n=48) Prednisone (n=50) Placebo group (n=52) Acyclovir 800mg 5 x/day x 21 days Prednisone 60mg/day x 1 st week, 30mg/day for days 8 -14, 15mg/day for days 15-21	<i>Analgesic were used:</i> Authors didn't mention the name Nobody used the narcotic analgesics	Side effects in <i>prednisone, acyclovir and placebo</i> group: Gastrointestinal symptoms, especially nausea and vomiting (21% of all patients) Edema, increased leukocyte counts, altered platelet counts, bilirubin levels, or hepatic function test result (2% of all patients) Serum aspartate glutamyl transferase levels > 50 U/L (9% of all patients) Hyperglycemia developed in 7 patients Side effects in <i>prednisone+ acyclovir</i> group: 1 patient died of myocardial infarction on study day 26 Side effects in <i>prednisone</i> group: 2 patients developed cutaneous dissemination Side effects in <i>acyclovir</i> group: 1 patient developed cutaneous dissemination Side effects in <i>placebo</i> group: 1 patient was hospitalized for bacterial pneumonia
Wood et al.[12] (1994)	7day acyclovir with 21-day Prednisolone (n=99) 7day acyclovir (n=101) 21day acyclovir with 21day Prednisolone (n=99) 21-day acyclovir without Prednisolone (n=101) Prednisolone 40mg/day for days0-6, 30mg/day for days 7-10, 20mg/day for days 11-14, 10mg/day for days 15-18, 5mg/day for days 19-21 Acyclovir 800mg 5xday	<i>No additional medication was given as co-intervention</i>	<i>Acyclovir + Prednisolone</i> group: (n= 198) (42 had side effects, 21%) <i>Acyclovir group + placebo:</i> (n=200 total) (24 had side effects, 12%)

Table 6. Summary of quality of evidence

Corticosteroids for preventing PHN					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Corticosteroids (95% CI)
Incidence of PHN (Corticosteroids versus carbamazepine)	58 (2 studies) 2 months	⊕ ⊕ ⊖ ⊖ LOW ^{1,2} due to risk of bias, inconsistency	RR 0.543 (0.087 to 3.376)	517 per 1000	236 fewer per 1000 (from 472 fewer to 1000 more)
Incidence of PHN (Corticosteroids versus placebo)	72 (2 studies) 4 weeks	⊕ ⊕ ⊖ ⊖ LOW ^{1,3} due to risk of bias, inconsistency	RR 0.990 (0.092 to 10.663)	316 per 1000	3 fewer per 1000 (from 287 fewer to 1000 more)

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.

3.3. Quality of the Evidence

The quality of the evidence was low due to high risk of bias and inconsistency of the results (unexplained heterogeneity in subgroup analyses with high $I^2 > 70\%$). (Table 6).

4. Discussion

All eligible studies were RCTs; 71% were double-blinded; the sample sizes ranged between 34 [8] to 349 [12], in all studies except one [12], the participants were immunocompetent adults above 50 years of age, the gender of the participants was reported except for Whitley, et al 10 in which it was only reported that slightly more than 50% of the participants were women. The participants in all the studies were diagnosed with early signs of herpes zoster. All seven studies used a corticosteroid (with or without acyclovir) in the prevention of post-herpetic neuralgia. Four studies provided data for the primary outcome (incidence of PHN), however due to the heterogeneity in comparison group (placebo, carbamazepine), subgroup analyses for corticosteroids versus placebo and corticosteroids versus carbamazepine are presented. There was moderate heterogeneity between the two studies comparing corticosteroids with carbamazepine; one study shows non-significant difference favoring corticosteroids [9] while the other study shows significant difference favoring carbamazepine [18]. The other two studies showed statistically significant heterogeneity comparing corticosteroids with placebo; one study showed non-significant difference favoring corticosteroids [8], while the other study showed a significant difference-favoring placebo [19].

Three electronic databases were searched (MEDLINE through PubMed, The Web of Science and The Cochrane Library). A limitation of this systematic review is the lack of access to EMBASE database. All included studies and reviews were manually searched for eligible studies. Overall, the results of this systematic review are applicable to both males and females as both genders were present in each of the reviewed studies. The mean age of the participants was between 55 to 73 years old when documented, most of the patients were Caucasian. Pregnant women, breastfeeding mothers and medically compromised patients (tuberculosis, diabetes mellitus, hypertension, cardiovascular diseases, lymphoma and leukemia) were often excluded from the studies. The included studies follow-up ranged from 6 weeks to over a yearlong therefore, some of the studies included in this review did address lingering effects, however, long-term (over one year) effects were not reported.

Only double-blinded RCTs were included in this review. All 7 studies were at high risk of bias. The evidence was low quality due to the high risk of the studies, the small number of studies included in each meta-analysis ($n=2$) and the inconsistency of the results (unexplained heterogeneity with high $I^2 > 70\%$), heterogeneity of the interventions, comparison interventions (placebo, acyclovir or carbamazepine) and the outcomes (incidence and severity of PHN; incidence, duration and severity of pain), all which made it impossible to compare many studies in one meta-analysis. Reviews published on the topic of corticosteroid efficacy in the prevention of PHN [20–30] agreed with our systematic review results; corticosteroids do not prevent PHN. Also, some reviews [30] were not able to interpret the effect of corticosteroids on PHN due to the poor quality of the evidence. Some reviews found acyclovir

better than corticosteroids [21, 26], however, others found that a combination therapy of antiviral medication (acyclovir) and corticosteroids may shorten the degree and duration of acute zoster pain [22, 23, 28, 29, 31]. All reviews agreed with this study in recommending further high quality studies to assess the effect of corticosteroids on both short-term pain and long term PHN.

5. Conclusions

In conclusion, there is no preventive intervention for PHN at present time. Healthcare providers can only treat PHN with palliative means and reduce the severity of the patients' pain. This systematic review found no conclusive evidence in favor of corticosteroids for the prevention of PHN, although some studies showed that corticosteroids may reduce pain severity and duration of the symptoms [9, 18]. Combination therapy with acyclovir has been shown to reduce the severity of PHN and increase quality of life [12, 14], as well as early intervention could be beneficial [32]. Reported side effects in the corticosteroids group were mild and reversible. Two serious cardiovascular events were reported in the combination therapy group, although the occurrence of these events was not reported to be a result of the therapy [13, 14]. Future research with multiple centers and homogeneous interventions, comparison groups and outcomes is needed. These trials need to assess long-term results and possible adverse risks in using corticosteroids for patients with herpes zoster [33].

Future studies should also include not only oral administration of the corticosteroid therapy but intravenous and muscular injections as well. Another confounding factor is age. The incidence rates are 10% in people above forty years and 20% to 50% for those above sixty years [10, 33]. However, the condition is rare in adults below the age of thirty. Adults above fifty years of age would likely show different responses compared to younger patients [11]. Adulthood comorbidities such as hypertension and osteoporosis, among others, may compound the results. The study period should not be limited to six months but instead to an extended time frame of not less than one year, so that long-term side effects of the therapy could be assessed. Future studies must consider combination therapy such as acyclovir with various preparations of corticosteroids, as combination therapy has shown promise.

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