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Efficacy and Safety of Corticosteroids in the Prevention of Post Herpetic Neuralgia: A Meta-analysis

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Abstract

The main objective of this meta-analysis was to evaluate the efficacy of corticosteroids in the prevention of post-herpetic neuralgia (PHN). Randomized control trials comparing corticosteroids versus control therapy (placebo) and corticosteroids plus standard therapy versus control plus standard therapy were included. Multiple databases were searched without any language restriction. Studies were included in accordance with the inclusion-exclusion criteria and were assessed for risk of bias. Eventually, seven studies were considered for qualitative and quantitative analysis and we were able to perform meta-analysis for only two compatible studies (193 subjects). The results showed moderate quality evidence that corticosteroids along with anti-viral agents administered during the acute phase of herpes zoster can prevent post-herpetic neuralgia six months after the onset of rash. Almost all of the studies included in this review evaluated pain severity but differed in the pain evaluation methods. Hence, we could not combine the data in our meta-analysis. There's no significant difference in the risks of serious adverse events associated with corticosteroids in comparison with placebo. Further high-quality studies are required in order to evaluate the efficacy of corticosteroids on both the short-term pain and long-term PHN.

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Introduction

Varicella zoster is a double-stranded DNA enveloped virus, which causes the childhood exanthema Varicella (chicken pox). Post-infection varicella zoster tends to go inactive in the dorsal root ganglia of the affected individual for a lifetime. Certain factors, such as a decrease in the host's immunity, stress and aging can reactivate the virus leading to a classic painful rash that is characteristic for herpes zoster. Initial symptoms such as paresthesia (in the involved dermatome) and pain often precede the skin rash by days to weeks [1]. Other symptoms include headache, light sensitivity and flu-like illness (without fever), which may be present before or along the course of the rash. The rash initially starts with the appearance of a confluence of vesicles, which later crust and eventually heal [2, 3]. After the skin lesion subsides, the pain may persist for a certain period of time (months to years) or for a lifetime and can profoundly impact an individual's quality of life. This chronic pain is commonly termed as post-herpetic neuralgia (PHN). PHN is immediate sequelae of herpes zoster and is diagnosed when zoster-associated pain continues to persist beyond ninety days after the onset of skin lesions [2, 4]. Increased patient age and degree of acute pain are associated with the development of PHN [5]. PHN may manifest in several forms such as pain, allodynia, paresthesia, dysesthesia and hyperalgesia [6, 7]. PHN is uncommon in people under 50 years but occurs in 20% of individuals between fifty and eighty years of age and the incidence increases to 35% in individuals >80 years of age [8, 9, 10]. The pain of PHN can be severe enough to affect all aspects of daily life [11]. Herpes zoster treatment comprises of three key aspects: (1) treating acute viral infection, (2) treating zoster-associated acute pain, and (3) preventing the development of PHN. Antiviral drugs, corticosteroids and accessory pain relief interventions are used for the above-mentioned purpose [12].

Over the course of time, various therapeutic interventions have been employed, but their effectiveness in alleviating the symptoms of established PHN is ambiguous [13]. Therefore, the development of more effective therapeutic interventions for preventing the development of PHN is a key area of current research. Based on their anti-inflammatory effects, corticosteroids are widely being used to deal with pain and inflammation during acute herpes zoster and to prevent the development of PHN [6]. The current consensus is that the early treatment of HZ results in less acute pain, accelerates the rash healing process, and reduces the incidence of developing PHN. However, prior studies which evaluated the efficacy of corticosteroids in the prevention of PHN provide contradictory results. Even with the lack of significant evidence in regards to their efficacy, corticosteroids are still widely included in the herpes zoster treatment and prevention of PHN. The main purpose of this study was to accomplish a meta-analysis so as to evaluate corticosteroids efficacy in preventing and treating post-herpetic neuralgia.

Materials and Methods

A comprehensive search was carried out in multiple databases such as Cochrane, Embase, MEDLINE (January 1960 to May 2018) for all relevant RCTs, which emphasized on the evaluation of the corticosteroids efficacy in the prevention of PHN (Fig. 1). We used the following keywords in identifying the most relevant articles for our study: herpes zoster, HZ, shingles, post-herpetic or post-herpetic, pain or neuralgia or neuropathy, PHN, corticosteroids, steroids, glucocorticoids, adrenal cortex hormones, triamcinolone', hydrocortisone, dexamethasone, prednisolone and prednisone. We only included those studies which met the following requirements : (1) RCT's with emphasis on prevention of PHN, (2) subjects with zoster-associated pain within 7 days of onset of dermatomal rash, (3) corticosteroids (dexamethasone, prednisone, triamcinolone, hydrocortisone, prednisolone) administered via oral, subcutaneous, intravenous and intramuscular route within seven days of the onset of the rash) and (4) trials which compared the efficacy of corticosteroids and standard treatment v/s placebo and standard treatment. The studies of RCT's with the topical administration or epidural injection of corticosteroids were excluded. In addition, quasi-RCTs, editorials, reviews, animal studies, case reports, pharmacokinetic trials, commentaries, and cost-effectiveness trials were excluded (Table 1). Two independent reviewers (first and corresponding author) screened all abstracts and titles from the multi-database search and in accordance with the criteria of inclusion decided to include or exclude an article for a full-text review, any disagreement was resolved by dialogue.

Data extraction from all the included studies was

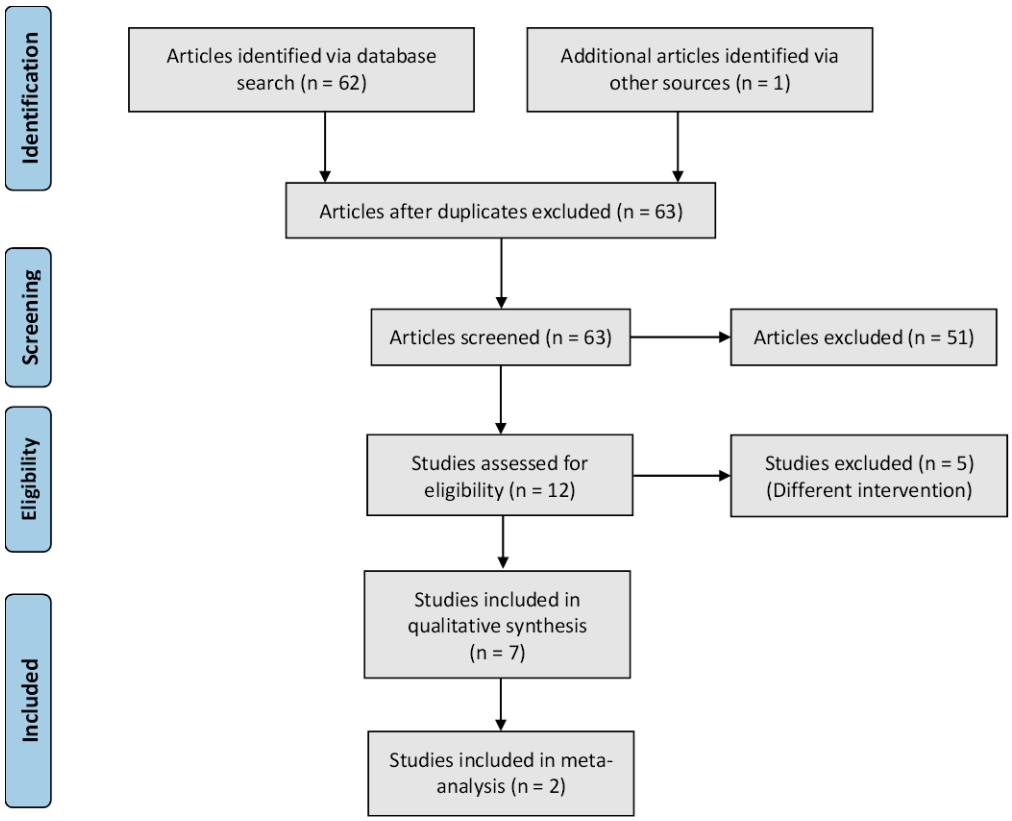

Fig. 1 PRISMA flow diagram of identification, screening, eligibility and inclusion of studies in the meta-analysis.

carried out by at least two independent reviewers and the acquired data (no. of participants, interventions, control treatment, outcome, and results) was entered into the Review Manager (RevMan 5), Cochrane statistical software. Any disagreement was resolved by dialogue.

As per the Cochrane collaboration standard scheme, two reviewers (first and corresponding author) evaluated the risk of bias that each RCT presented [14]. All eligible studies were assessed and adjudged as "High risk of bias", "Low risk of bias" or "unclear risk of bias". In case, there was inadequate data to evaluate the risk of bias, such studies were regarded as the unclear risk of bias (Fig. 2). Any disagreement was resolved by dialogue. The primary outcome of the current meta-analysis was the existence of PHN six months after the onset of the acute herpetic rash. Fundamentally, PHN was defined as persistent or recurrent pain in the area of herpes zoster thirty days after the onset of the herpetic lesions [15]. There were three specific measures for the secondary outcome as documented by studies included in this meta-analysis: (1) intensity of pain, as estimated by a validated visual analog scale after 3, 6 and 12 months. (2) Short Form – 36 health survey questionnaire was used to measure the quality of life after six months [16], and (3) undesired outcomes during the study or within fourteen days post cessation of treatment. They were categorized as serious or non-serious. Events which were life threatened life or prolonged hospital stay or caused death were classified as serious adverse events.

As per the GRADE criteria, the findings from each of the included RCT's was evaluated and adjudged as high, moderate, low or very low quality [17]. Risk ratios with 95% confidence intervals were calculated for individual eligible studies and for the combined pooled result. Statistical heterogeneity among trials was evaluated by Chi^2 test with a 10% level of statistical significance (P 0.1) and $I^2 > 50\%$ [18, 19]. Random effects model was used when unexplained heterogeneity was found, or else a fixed-effect model was used for meta-analysis. Sub-group analysis is documented for studies comparing corticosteroids against placebo.

Table 1 List of excluded studies in the meta-analysis.

Study	Reasons for exclusion
Keczkes et al. 1980	RCT, but carbamazepine was used to treat the control group
Bernoldi et al. 1991	RCT, but carbamazepine was used to treat the control group
Brusco et al. 1993	Non- RCT
Xu et al. 1999	Trial exceeded treatment within 7 days of onset criteria
Li et al. 2000	Non- RCT
Yang et al. 2000	Mismatched routine treatments
Ma et al. 2000	Non-RCT
Zhou et al. 2000	Non-RCT
Rice et al. 2001	Non- RCT
Guo et al. 2001	Mismatched routine treatments
Li et al. 2002	Non-RCT
Hao et al. 2002	Non-RCT
Cui et al. 2002	Non-RCT
Lin et al. 2002	Trial exceeded treatment within 7 days of onset criteria
Ma et al. 2002	Non-RCT
Yang et al. 2002	PHN = pain persisting 14 days post onset of rash
Hughler et al. 2002	Non-RCT
Zhang et al. 2003	Non-RCT
Liu et al. 2003	PHN = pain persisting 14 days post onset of rash
Torre-M et al. 2003	Non-RCT
Huang et al. 2004	Non-RCT
Wang et al. 2004	Trial exceeded treatment within 7 days of onset criteria
Tang et al. 2004	Non-RCT
Yin et al. 2004	Mismatched routine treatments
Zhang et al. 2004	Mismatched routine treatments
Zheng et al. 2004	Mismatched routine treatments
Opstelten et al. 2004	Non-RCT
Chang et al. 2004	PHN = pain persisting 14 days post onset of rash
Zhang et al. 2005	Trial exceeded treatment within 7 days of onset criteria
Jiang et al. 2005	Mismatched routine treatments
Yin et al. 2005	Mismatched routine treatments
Liu et al. 2005	PHN = pain persisting 14 days post onset of rash
Liao et al. 2005	PHN = pain persisting 7 days post complete decrustation
Lin et al. 2005	Non-RCT
Van Seventer et al. 2006	Mismatched routine treatments
Jiang et al. 2008	Non-RCT
Zhou et al. 2008	Non-RCT
Shi et al. 2008	Non-RCT
Song et al. 2009	Non-RCT
Liu et al. 2009	Non-RCT
Backonja et al. 2009	Mismatched routine treatments
Yang et al. 2010	Non-RCT
Huang et al. 2010	Non-RCT
Zeng et al. 2011	Non-RCT
Rice et al. 2014	Non-RCT
Meulenhoff et al. 2014	Non-RCT
Xu et al. 2014	Mismatched routine treatments
Zhang et al. 2014	Mismatched routine treatments
Zhang et al. 2015	Mismatched routine treatments
Schug et al. 2017	Non-RCT
Bertrand et al. 2017	Non-RCT
Rulln et al. 2017	Unclear

Results

The multi-database search identified a number of relevant articles. After screening the titles and abstracts, 63 possible RCTs were selected. 51 studies were initially excluded (Table 1.). Later on, five studies were excluded. Eventually, seven studies satisfied the inclusion criteria and all of them were RCT's, double-blind, placebo-controlled parallel studies with a cumulative aggregate of 980

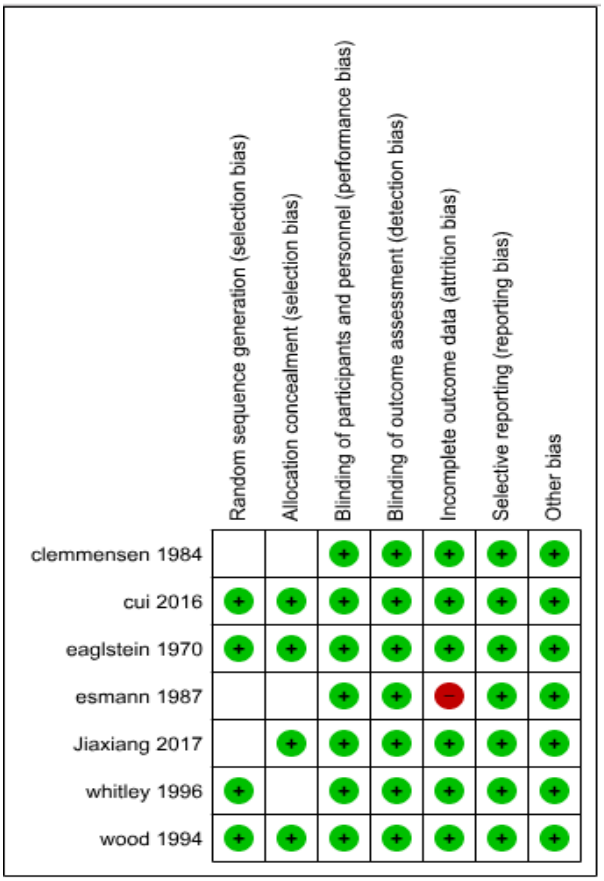

Fig. 2 Risk of bias in included studies.

subjects. [20-26]. All subjects in six trials were adults and their age ranged from 50 to 91 years old [20-25]. Info regarding the gender (male 307, female 427) and mean age of the subjects was reported by four trials [22, 24-26]. The time of onset of rash to the commencement of treatment was 0-7 days for six included studies [20-22, 24-26]. Two studies compared glucocorticoids to a placebo [22, 23]. Five compared standard treatment (antiviral +/- analgesic) with or without concomitant glucocorticoid [20, 21, 24-26]. The risks of bias in all seven studies are shown in Fig. 2. Out of the seven included studies, six of them [20, 21, 23-26] provided the incidence of PHN at six months post onset of herpetic lesions while one study [22] did not and had to be excluded from the meta-analysis. Details regarding total no. of subjects with PHN at six months post onset of herpetic lesions were not provided by two studies [25, 26] and hence were excluded from the meta-analysis. Undesired outcome within fourteen days post cessation of treatment was documented by all seven studies [20-26].

Effects of interventions

Primary outcome measure

The data regarding the existence of PHN six months post the onset of herpetic lesions was obtained from a study comparing the efficacy of corticosteroids against a placebo [23]. The results of this study indicated no obvious difference in the presence of PHN six months post onset of hepatic lesions in the steroid group (2/15, 13.3%) in comparison to the placebo group (2/20, 10.0%). However, wide confidence intervals meant significant benefit or harm (RR 1.33, 95% CI 0.21 to 8.41) cannot be excluded. Another trial [24] compared corticosteroid and standard treatment versus placebo and standard treatment and no obvious difference in the presence of post-herpetic neuralgia six months post onset of rash between the corticosteroids and antiviral agents group (9/42, 21.4%) in comparison to the placebo and antiviral agents group (9/37, 24.3%; RR 0.88; 95% CI 0.39 to 1.98) (Fig. 3). Another two trials [20, 21] also compared corticosteroid and standard treatment versus placebo and standard treatment and statistically significant difference was observed in the presence of PHN six months post onset of rash in the steroids and antiviral agents group (2/50, 4% and 2/47, 4.2%) in comparison to the placebo and antiviral agents group (9/50, 18% and 9/46, 19.5%; RR 0.22 and 0.22; 95% CI 0.05 to 0.98 and 0.05 to 0.95). By pooling the data from the above mentioned two trials [20, 21] with a cumulative aggregate of 193 subjects, a meta-analysis was conducted and the results indicated that oral steroids along with anti-viral agents played a moderately significant role in preventing the occurrence of post-herpetic neuralgia six months post onset of herpetic lesions (RR 0.22, 95% CI 0.08 to 0.63, P= 0.005) (Fig. 4).

Secondary outcome measures

Pain severity measured by a visual analog scale after 3, 6 and 12 months

Five of the included trials [20, 22-26] assessed the severity of pain after administering steroids to treat herpes zoster. This data was recorded by four of them only for one month using the pain assessment methods and their use differed from each other. Hence we could not include this data in the meta-analysis.

Quality of life

Unfortunately, none of the studies used the SF-36 Health Survey to provide data on quality of life post

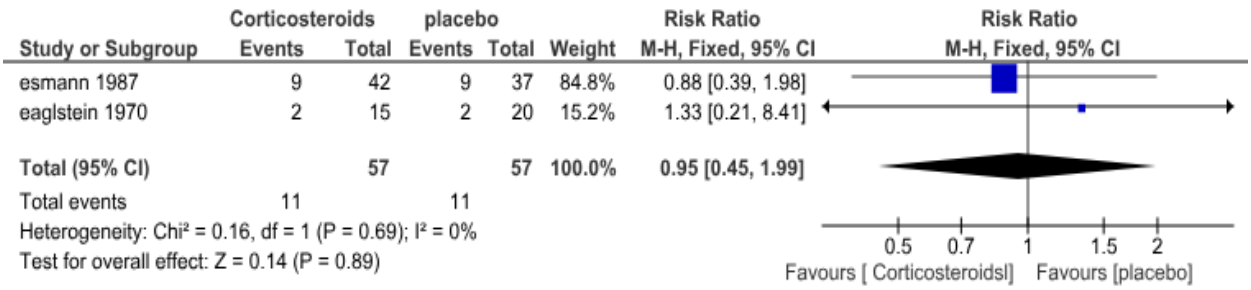

Fig. 3 Comparison of the effect of corticosteroid versus placebo on the presence of PHN six months post onset of herpetic lesions via forest plot.

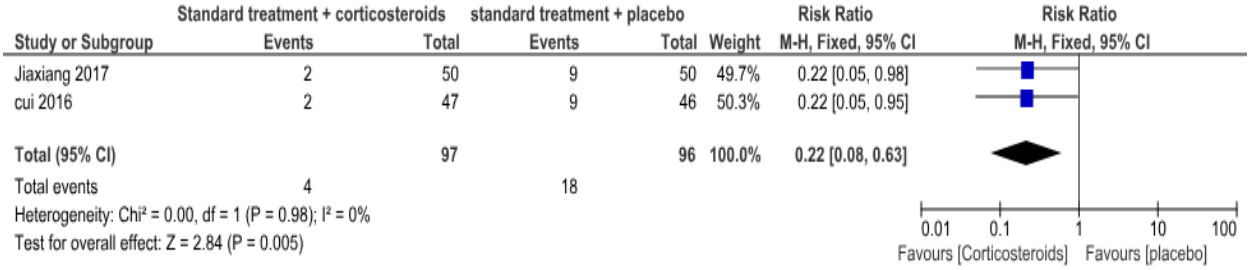

Fig. 4 Comparison of the effect of standard treatment + corticosteroid versus standard treatment + placebo on the presence of PHN six months post onset of herpetic lesions via forest plot.

6 months.

Undesired outcomes within fourteen days post cessation of therapy

Serious adverse events

Four studies reported the absence of serious adverse effects which can be attributed to experimental treatment [20-23]. Three studies provided details of serious adverse events within fourteen days post cessation of treatment and these included myocardial insufficiency [24], MI and bronchopneumonia [25], chest infection, hematemesis and death from undisclosed causes [26]. The incidence of serious adverse events for corticosteroids (6/423) was found to have a slight difference in comparison to that of placebo (2/423) (RR 2.28, 95% CI 0.59 to 8.76, P= 0.23) (Fig. 5).

Non-serious adverse events

Details were provided by five trials [20, 22, 23, 25, 26] and they were GI symptoms (nausea, vomiting, and diarrhea), dizziness, headaches, edema, hyperglycemia, and an increase of serum aspartate glutamyl transferase. There was no statistically obvious difference in the overall incidence of non-serious adverse events among corticosteroids (63/422) and placebo groups (46/427) with (RR 1.39, 95% CI 0.99 to 1.97, P= 0.06) (Fig. 6).

Discussion

The central objective of this meta-analysis was to review the empirical evidence that has been obtained from relevant RCTs regarding the efficacy and safety of corticosteroids in the prevention of PHN. A total of seven trials with a total of 980 subjects, assessing the efficacy and safety of corticosteroids in preventing the occurrence of PHN were included. However, it is a relatively small sample size in relation to the known variability in the outcome of PHN. The meta-analysis of two included studies that documented the primary outcome of this review indicated a moderately significant difference in the presence of PHN six months post onset of rash between the steroid with antiviral subjects and the placebo with antiviral subjects. However, regarding cessation of pain, there was no obvious difference in four larger trials with a cumulative aggregate of 753 subjects [20, 21, 25, 26].

Established PHN may interfere with various aspects of an individual's life. Pain evaluation is one of the main aspects of dealing with neuralgia. Dermatologists and physicians must perform a detailed pain assessment during the period of treatment and follow-up, which must include the nature, severity, location and pain score. VAS and

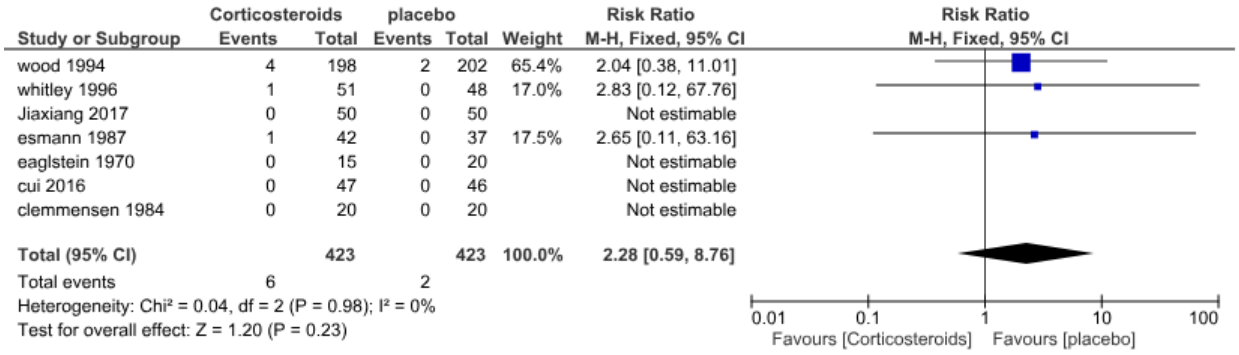

Fig. 5 Comparison of serious adverse events in corticosteroids versus placebo via forest plot.

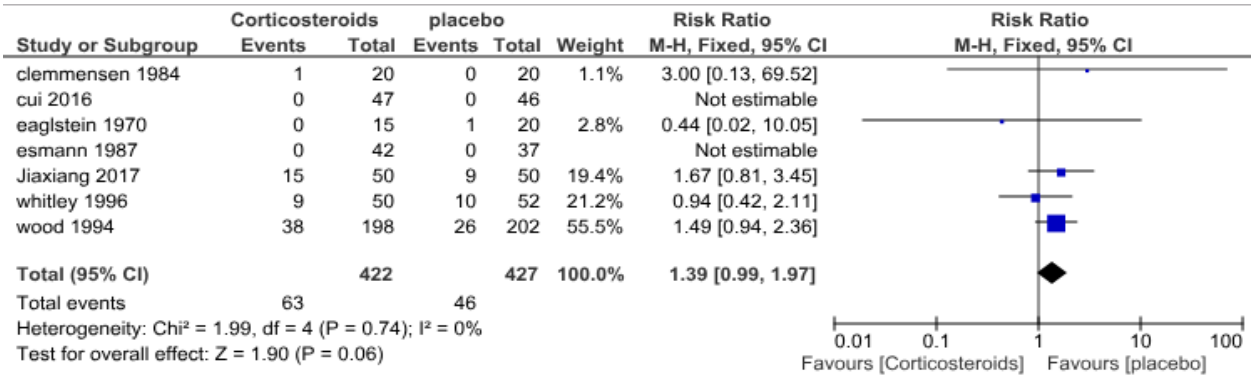

Fig. 6 Comparison of non-serious adverse events between corticosteroids and placebo via forest plot.

NRS are the most common pain evaluation methods. Almost all of the included studies assessed the severity of pain but differed in the pain assessment methods. Hence, this data could not be included in our meta-analysis. Two trials [22, 24] documented that there was no additional pain relief after treatment with corticosteroids during the three or six months of follow up. Three trials [20, 21, 23] documented spontaneous resolution of pain without any therapy; however, more rapid resolution of pain was observed with steroid therapy. The results of these three trials indicate that steroids may play a key role in accelerating healing and reducing zoster-associated pain. However, this conclusion differs from the lack of effect of corticosteroids on the persistence of PHN and suggests that the relationship between acute inflammation, pain and PHN is complicated. All seven included studies documented undesired outcomes, but they were not significantly more common in corticosteroid than in placebo subjects.

Conclusions

Based on the evidence from all the included trials, the authors would like to conclude that short courses of corticosteroids do not result in significantly more adverse events in participants with acute herpes zoster but they are ineffective in preventing PHN persists at six months. There is moderate quality evidence, which supports the use of corticosteroids along with antiviral agents in acute herpes zoster infection for preventing PHN. However, larger trials with sufficient sample size will be able to detect a meaningful difference if they can include validated and approved pain outcomes. Further high-quality studies to assess the effect of corticosteroids on both the short-term pain and long-term PHN are required. This may provide information about the mechanisms of transition from acute pain to long-term PHN.

Conflict of Interest

The authors declare that we have no conflict of interest to declare.

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