



Efficacy of Corticosteroids in the Prevention of Post Herpetic Neuralgia

Abstract

The available empirical and research evidence suggests that Postherpetic neuralgia (PHN) is a typical serious medical complication associated with herpes zoster (HZ; Chen 2010). Notable, it has been reported that anti-inflammatory properties of corticosteroids could be beneficial in the prevention of PHN (Chen 2010). The core objective of this review was to examine the effectiveness of corticosteroids in the prevention of PHN.

The researchers evaluated the studies for the relevant randomised controlled trials (RCTs) of corticosteroids for PHN prevention in Google Scholar, ClinicalTrials.gov, EMBASE, MEDLINE, and Cochrane Library databases. The timeframe was restricted to the studies published between 3 February 2010 and March 26, 2018. The rationale for this restriction was to determine whether recent studies have contributed similar or conflicting empirical evidence to Chen's (2010) Cochrane review. The present review included all the RCTs that involved administration of corticosteroids in different forms, including intravenous or intramuscular, to patients diagnosed with herpes zoster (HZ). We identified relevant articles, obtained the data and three independent reviewers evaluated each RCT's quality. Lack of consensus in data extraction was addressed through discussion. Assessment of the five articles included in the present review showed that a treatment intervention involving corticosteroids does not significantly prevent or mitigate the pain that is associated with PHN.

Background

Herpes zoster (HZ) is typically described as a debilitating and painful condition "caused by a reactivation of the varicella-zoster virus (VZV) from a latent infection of sensory ganglia" (Johnson 2010). Mainly, the symptoms of this disease are often not specific and can range from an intense burning sensation to itching (Jeon 2015). Research has demonstrated varicella-zoster virus acquired during chicken pox contributes towards the reactivation of HZ, which notably is the major varicella infection (Chen 2010). It is important to note that empirical research and evidence has also revealed that the latent VZV reactivation from the dorsal ganglia is usually responsible for the traditional dermatomal rash and pain that is associated with HZ (Chen 2010; Gershon 2010; Johnson 2010; Puri 2011).

The vesicular skin rash in the affected dermatome, which is often accompanied by acute pain, is considered to be the acute phase of the HZ condition (Johnson 2010; Gan 2013). The acute phase of HZ is often described as occurring up to 30 days after the onset of the rash (Jeon 2015). The patients who later develop chronic disease usually experience a subacute phase that lasts between 30 and 90 days after the onset of the vesicular skin rash in the affected dermatome (Johnson 2010). Compared to the other side effects associated with HZ, PHN is reported to be the most troublesome (Jeon 2015). Nevertheless, PHN often exhibits a considerable degree of resistance to the existing analgesic treatments, for example, anticonvulsants, opioids, antidepressants, and topical agents, such as capsaicin cream and lidocaine patches, and thus it can persist for many years (Jeon 2015).

It is believed that the early diagnosis and treatment of acute HZ with suitable antiviral agents reduces its severity and more importantly, mitigates the risk of PHN (Whitley 2010; Jeon 2015). It

has been suggested that the prophylactic vaccination against VZV could potentially be the ideal way to prevent as well as minimize the incidence of PHN and HZ (Jeon 2015). On the other hand, corticosteroids possess a potent anti-inflammatory action that can minimize nerve damage and thereby prevent or relieve the pain in individuals that have been diagnosed with PHN (Chen 2010; Massengill 2014). Adding corticosteroids to treatment with acyclovir reduces the pain of HZ and increases the pace at which skin lesions heal (Fashner 2010). In fact, it is recommended that a combination therapy of antivirals and corticosteroids should be used on older patients without contra-indications.

In a 2010 Cochrane review, it was observed that although corticosteroids possess anti-inflammatory effects that are capable of reducing nerve damage and the risk to PHN, there is no significant distinction between placebo and corticosteroids in preventing PHN symptoms after the onset of the common dermatomal rash and pain associated with HZ (Chen 2010). It is worth noting that the treatment of HZ has three key objectives: 1) prevention of the PHN, 2) treatment of the acute pain that is openly associated with HZ, and 3) treatment of the acute infection (Chen 2010). Research and empirical evidence have confirmed that antiviral agents and adjunct medications, including oral corticosteroids, tricyclic antidepressants, and opioid analgesics, can relieve the pain associated with HZ and consequently, therapy using these drugs can achieve the mentioned three significant objectives of treating HZ (Chen 2010; Fashner 2010). However, other similar studies have shown that these antiviral agents and adjunct medications lack a significant benefit in preventing or reducing the pain associated with HZ. Surprisingly, lack of clear empirical evidence about the effectiveness of corticosteroids has not stopped or reduced the widespread use of these medications in the treatment of HZ (Chen 2010). Thus, a review on the efficacy of corticosteroids in prevention of PHN is critical in clinical practice, especially in the contemporary medical field where evidence-based practice (EBP) is a mandatory requirement in patient care and treatment. The objective of this review was to examine the corticosteroids' efficacy in preventing PHN.

Materials and Methods

We searched multiple comprehensive databases with the objective of finding the most relevant studies that have placed an emphasis on evaluating the effectiveness of corticosteroids in preventing PHN (Chen 2010). In particular, the research design employed that the present review was based on the Cochrane Review Methods (Higgins 2011). The findings drawn from the review were reported in accordance with the 2015 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher 2010; Shamseer 2015).

Literature and Data Sources for the Review

We conducted the search for this review on March 26, 2018. In particular, we searched Google Scholar, ClinicalTrials.gov, EMBASE, MEDLINE, and Cochrane Library databases (Chen 2010). The researchers in the present study included both the published RCTs (Chen 2010). We applied date restrictions to all our electronic searchers. Only articles that were published in the period between February 3, 2010 and March 26, 2018 were considered for the review. Nevertheless, we did not apply language restrictions to the electronic searches. Specifically, we used the following keywords to identify the most relevant articles for our review: herpes zoster, HZ, postherpetic neuralgia, PHN, efficacy, effectiveness, corticosteroids, shingles, glucocorticoids, prednisolone, prednisone, postherpetic, triamcinolone, post-herpetic, pain, steroid, neuralgia, dexamethasone, adrenal cortex hormones, hydrocortisone, and neuropathy (Chen 2010). Meanwhile, we also used the following Boolean operators in developing appropriate combination of the search terms: OR, NOT, and AND. Upon completing the initial electronic search, we examined the identified sources to determine whether or not there were articles that were relevant to the present review. The scientific publications in the reference lists of the identified articles on RCTs were separately

examined for inclusion into the study.

Selection of Studies

We evaluated all the articles that could be suitable to our study; two independent reviewers (X and D) assessed the relevance of data from the articles using predefined criteria. In the event there was a disagreement between the two reviewers on whether or not a particular study should be included in the review, the consensus approach was used to reach an agreement. The independent reviewers used the title and abstract to determine the relevancy of the identified articles, i.e. to establish the study's background, objectives, research method, key findings, and conclusions. Moreover, the reviewers assessed the full text of all potentially relevant articles. Articles were included in the present review if they satisfied each of the following requirements: 1) RCTs that included participants that had been diagnosed with HZ within 3 weeks after the herpetic skin rash first appeared; 2) the control group in the study received oral corticosteroids as well as the standard medical therapy; 3) the intervention group received the standard medical therapy and with the exception of corticosteroids, all other relevant drugs used in the management of pain; 4) data was collected in less than 24 weeks after the final treatment intervention.

The Extraction

Data extraction from the included articles was carried out by at least three independent reviewers. The two reviewers independently entered the two acquired data into a Review Manager (RevMan 5). In case there was a discrepancy in the extracted data, the reviewers engaged in a discussion that was aimed at resolving the conflict. However, in the event that the data discrepancy issue remained unsettled after sufficient discussion among the three independent reviewers, the fourth independent reviewer was invited to resolve the discrepancy. The decision of the fourth reviewer concerning the discrepancy was considered final. In particular situations, we contacted the study authors to inquire and request some specific data. We used e-mail addresses and phone contacts contained in the articles to initiate correspondence with the authors of the different studies.

The data that the independent reviewers obtained or extracted from the identified studies included titles of the researches, name(s) of the author(s), criteria for inclusion and exclusion in the research, period that the investigation was carried out for, number of participants, nature or group of the administered corticosteroids, adverse events, outcomes of the study, and the number of patient withdrawals that were associated with treatment interventions. The primary outcome measure for the present review was PHN presence 24 weeks after the onset of the acute herpetic rash. Fundamentally, we determined the presence of PHN based on the standard criteria for clinical diagnosis (pain continuing or pain recurrent) at the site of the shingles at least 4 weeks after the onset of the rash that was acute (MacDonald 2000). At the same time, the secondary patients' outcomes were similar to those suggested by Chen (2010) in their Cochrane review titled "Corticosteroids for preventing postherpetic neuralgia."

Three independent reviewers evaluated the risk of bias that each RCT presented. The examination of the prejudice risk was performed taking into consideration various parameters, including security of the randomization used in the study, selective result reporting, wholesomeness of the outcome data, allocation concealment, and all other potential sources of study bias. The 3 independent reviewers used the standard scheme that has been developed by Cochrane Collaboration to assess the degree of bias in each of the articles (Higgins 2008).

The present review had three specific measures for the secondary outcomes. First, the level of pain was measured by an authenticated statistical vivid scale or visual analog scale after twelve, 24, and 48 weeks. Second, the quality of life was measured using short form 36 questionnaire (SF-

36) after 24 weeks (Chen 2010). Finally, we measured the detrimental occurrences that took place in course of 2 weeks after ending the treatment interventions. We considered severe negative incidents, for example, those that were life-threatening, presupposed hospitalization, or caused death.

Analysis of Data Using Statistical Methods

The central finding of the present review, as was pointed out earlier in the discussion was PNH presence 24 weeks after the acute herpetic rash has set in. It is worth pointing out that although the PNH condition is often defined as pain persisting in three or more than three months after the onset of the disease, the pain can, in fact, last longer (Achar 2012). Hence, in order to examine the efficacy of corticosteroids in management of persistent pain for long periods in patients that had been diagnosed with PNH, it was crucial for us to explore the disease outcomes 24 weeks and 48 weeks after the final treatment intervention. The outcomes that were secondary to the research included measuring the level of pain based on a relevant gauge and the patient's quality of life before and after the patient was given corticosteroids. We measured the intensity of pain at weighted mean distinctions and 95% CIs. The average and the standard deviation values of the computed intensity of pain reported in each of the included studies were calculated using the invariance variance and random effects modeling. Since the pieces of empirical evidence used various types of scales to measure the intensity of pain, we used the mean differences as the ideal statistical tool for standardizing the values that had been received from each of the independent scales that were used in different studies. Moreover, with regard to studies that were included in this research, we computed the standard deviation from the range of the particular values using the relevant equations that have been included in the Methods of Cochrane.

Results

Identification of Studies

In course of the search for the most relevant articles, a total of 656 articles were identified (Fig. 1). The specific number of articles obtained from each of the databases is as follows: 59 from Google Scholar, 184 from ClinicalTrials.gov, 216 from EMBASE, 102 MEDLINE, and 95 from Cochrane Library. Of these, we excluded a total of 648 articles that did not satisfy the inclusion criteria. We obtained the full texts of the remaining 8 articles. However, after subjecting the 8 articles to a more in-depth analysis, we discovered that 3 articles had to be excluded for a number of reasons. Two articles used a cross-over design as opposed to the RCT design and the other article did not provide insights on the PNH incidence. It was worth mentioning that we did not find new RCTs after examining the references of the included 5 articles.

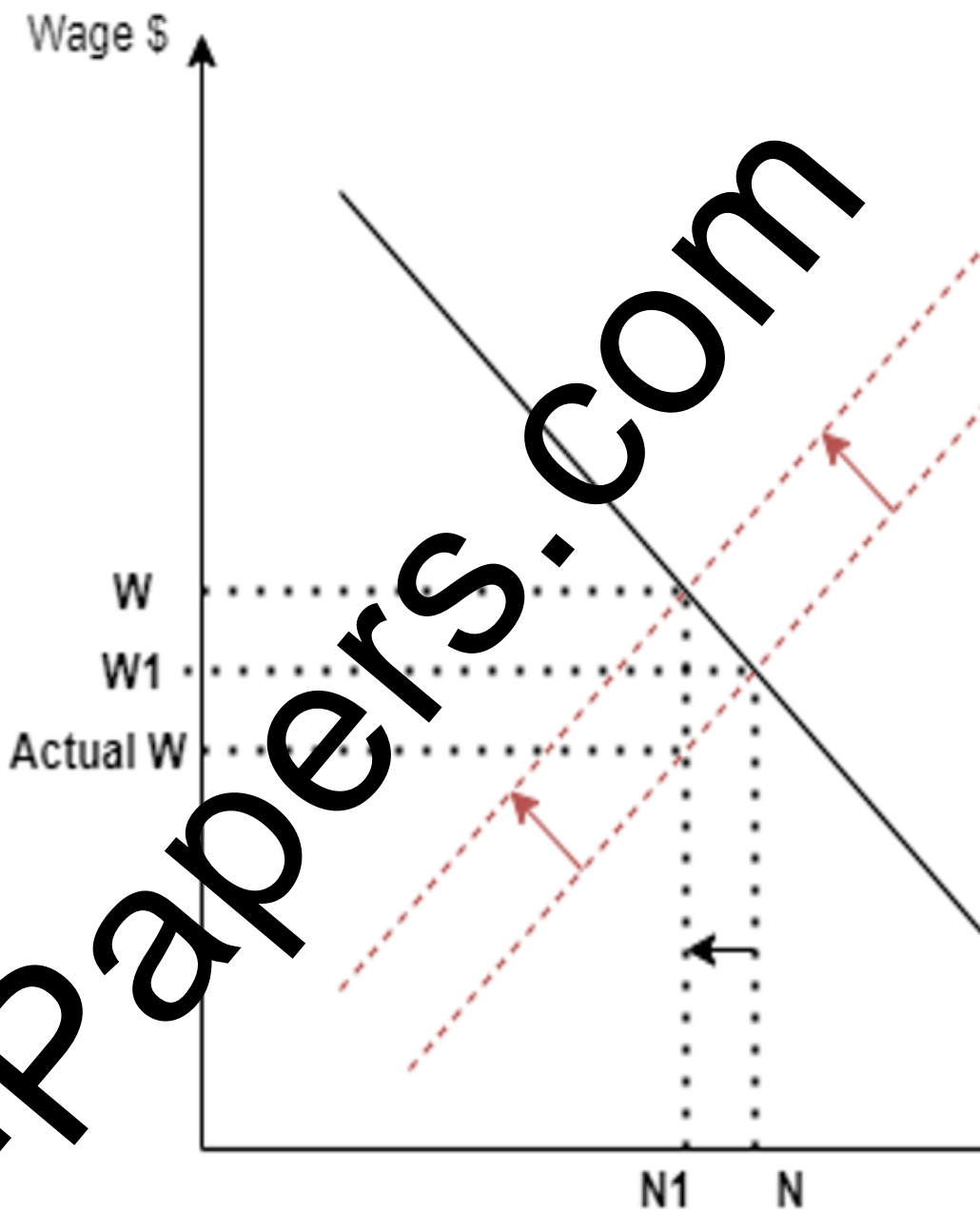


Figure 1. Search strategy framework

Characteristics of the Patient Populations and the Studies

All the studies that were included in this review were RCTs. The significance of including only the studies that had used RCT design was informed by the fact that this research design often yields valid and reliable outcomes as it ensures that the degree of research bias is minimal. The participants in each of the included studies had been diagnosed with PNH, and thus, the treatment intervention, the primary outcomes, and the secondary outcomes that the present review aimed to examine were all consistent with both the goals and objectives of the research.

Quality of the Included Studies

The uniformity of the RCTs that were included in the present review was significant in the context of PHN incidence. Nevertheless, we evaluated the health outcomes in each of the subgroups

based on the type of corticosteroids and therapy that was administered to the patients. Mostly, this assessment revealed that the heterogeneity between the RCTs that were included in this review was insignificant ($I^2 < 30\%$). It is worth pointing out that although the quality of some of the articles was relatively low, lack of high-quality RCTs forced us to include these articles in the present review. The rationale for taking this approach was primarily informed by the fact that there were insignificant differences in the study outcomes, particularly those that were relevant to the present review. The risk of bias in each of the included articles was reduced with the help of a computer program that randomly assigned the participants to the groups with various treatment interventions. It is worth mentioning that although the detailed approaches that the researchers used to allocate the participants the groups for the treatment interventions were not clear in some of the articles, a critical evaluation of each of the included articles showed that the demographic characteristics of both the control and the intervention groups were similar. Therefore, this provided a basis for concluding that the included articles were both valid and reliable as far as meeting of the objectives and goals of the present study was concerned.

Table 1: Summary of the risk of bias in the included articles

Study	Random Sequence	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall bias
Alexander (2017)	??	++	++	---	++	??	++
van Wijck (2011)	??	++	---	++	----	----	++
Chen (2010)	??	++	----	++	??	??	++
Lynch (2011)	----	----	----	----	----	----	++
Achar (2012)	---	??	??	??	----	----	++

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

It has also emerged from the detailed evaluation of the included articles that the demographic attributes of the participants were dissimilar between trials.

Discussion

The central goal and objective of the present review was to critically analyze the empirical evidence that has been published between February 3, 2010 and March 26, 2018 to determine whether or

not the administration of corticosteroids is an effective therapy for the prevention of PHN. In the 2010 Cochrane review, Chen (2010) reported that although corticosteroids possess anti-inflammatory effects that can reduce nerve damage as well as the risk to PHN, there is no significant distinction between placebo and corticosteroids in preventing PHN six months after the onset of the common dermatomal rash and pain associated with HZ. Chen (2010) acknowledged that although there is no clear and indisputable research and empirical evidence that corticosteroids can effectively stop or reduce the pain associated with PHN, a substantial number of people continue to use this drug. Hence, this review placed a considerable emphasis on evaluating the studies that have been published after Chen's (2010) Cochrane review "Corticosteroids for preventing postherpetic neuralgia" to establish whether or not the studies that have been carried out after February 3, 2010 have reported conflicting outcomes with regard to the efficacy of corticosteroids in the prevention of PHN.

A detailed analysis of the data extracted from the five RCTs included in this review showed that there was an insignificant difference in the number of the study participants that had been diagnosed with PHN 24 weeks after the onset of the vesicular skin rash between the patients in the control group and the placebo group. Analysis of the data obtained from the included articles also showed that PHN could be a complex condition that can, in some cases, lead to an inability of taking part in both domestic and social activities (Alexander 2017). Thus, it is crucial for practitioners and scholars to invest heavily in developing and adopting an EBP treatment intervention for PHN. In the contemporary medical setting, the numerical descriptive scales (NRS) and validated visual analog scales (VAS) are the most common methods used in the assessment of pain associated with PHN (van Wijck 2011). In the included articles the evaluation of changes in pain intensity was conducted using different methods for pain evaluation. Thus, like Chen (2010), we were also unable to compare the extracted data on pain intensity changes in the present review. It was incredibly problematic for us to identify and use an appropriate statistical tool to analyze the data from the different scales. Each of the included articles confirmed that corticosteroid treatment administered to patients that have been diagnosed with PHN does not provide significant pain relief. Consequently, this finding is consistent with that of Chen (2010) in their Cochrane review. It is explicit from the empirical evidence in this review that although corticosteroids possess characteristics that can potentially be used to prevent PHN, the link between the usage of these drugs and treatment of the pain associated with PHN is intricate. Therefore, it is important for scholars and medical practitioners to urgently direct their attention towards developing a treatment intervention that best suits the elimination of the pain associated with PHN.