



Review article

Oral Chinese herbal medicine for post-herpetic neuralgia: A systematic review and meta-analysis of randomized controlled trials



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ABSTRACT

Introduction: Post-herpetic neuralgia (PHN) is a common complication of herpes zoster. Pain medications have shown benefit, however many patients do not achieve adequate pain relief. Oral Chinese herbal medicine (CHM) has been used for people with PHN but its benefit is unclear. This review examined the efficacy and safety of oral CHM alone or as add-on therapy for PHN.

Methods: Nine English and Chinese databases were searched from their inceptions to March 2016. Randomized controlled trials (RCTs) evaluating oral CHM for PHN were included. Methodological quality was assessed using the Cochrane Collaboration's risk of bias tool. Data were analysed using Review Manager software.

Results: Twelve RCTs involving 853 participants were included with low to moderate quality based on risk of bias assessment. Oral CHM as an add-on intervention to pharmacotherapy improved visual analogue scale (VAS) pain score (MD -1.88 cm [-3.34 to -0.42], $I^2 = 98\%$), and scores on the Hamilton Rating Scale for Depression (HAM-D) (MD -2.45 points [-3.70 to -1.20], $I^2 = 13\%$) compared with pharmacotherapy alone. Significant changes from baseline were seen for all groups. No severe adverse events were reported.

Conclusions: These findings suggested that oral CHM in addition to pharmacotherapy may be beneficial for patients with PHN. Oral CHM alone or combined with pharmacotherapy appeared to be safe. More high quality trials with rigorous research methods are needed.

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1. Introduction

Post-herpetic neuralgia (PHN) is a common complication of herpes zoster (HZ), affecting between 10 and 20% of people over 50 years of age [1]. The incidence rises with advancing age, and has been reported to be nearly 80% in people 80 years or older [2]. Pain may be present continuously or intermittently, and is usually limited to the same dermatome in which the herpes zoster rash occurred [3]. Pathological changes of both central nervous system and peripheral nervous system may contribute to the neuralgia [4–6]. Pain is described as burning, aching, throbbing, lancinating or electric-shock like [7] and can be associated with other symptoms such as sleep disturbance, loss of appetite, weight loss, and depression [8].

The impact of PHN is significant [4], due to decreased quality of life, and increased costs associated with the treatments [9]. People with PHN experience worse general wellbeing than those without PHN. The impact of chronic pain on mental health is considerable, with up to 43% of people suffered from chronic pain were reported with moderate levels of anxiety or depression [10]. Health care utilisation in people with PHN is also high, with an average of 11.9 visits to general practitioners to manage pain [11].

Clinical practice guidelines for PHN [12] and chronic pain (which include specific reference to PHN) [13–15] recommend tricyclic antidepressants (TCAs), gabapentin, and pregabalin as first line treatment for PHN. Variation exists in additional first line treatments and second line therapies, and include opioid analgesics, tramadol and topical lidocaine. All medications have been shown to be effective, however the individual response varies considerably. Between 40 and 50% of people with PHN do not respond to any treatment [16], and many people taking multiple medications continue to experience pain most or all of the time [17]. Many of the guideline recommended pharmacotherapies used in the included studies have established safety profiles and known adverse events (AEs). For example, sedation, dry mouth, blurred vision, weight gain and urinary retention were reported with TCAs; dizziness, sedation and peripheral edema were seen with anticonvulsants (gabapentin and pregabalin); and nausea, vomiting, constipation, sedation, dizziness, seizures and postural hypotension were common with tramadol [4].

Effective pain relief is difficult to attain for patients and clinicians, and is an area of unmet clinical need [8]. Some authors have included a minimum threshold for clinically important pain of three on a 10-point scale [18,19]. Dubinsky et al. [12] considered that a reduction in VAS or Likert scale to below four, or by 50%, was adequate pain relief. Currently, no minimal clinically important difference (MCID) has been defined for PHN.

Chinese herbal medicine (CHM) has a long history of use in China. CHM has been used to treat a range of pain related conditions, and has been evaluated in a Cochrane systematic review of neuropathic pain [20]. In people with diabetic peripheral neuropathy, CHM produced greater global improvements in pain

and numbness than conventional medicine [20], although the review authors noted the poor methodological quality of included studies and lack of objective outcome measures. One systematic review evaluating Chinese medicine (CM) for PHN was identified in Chinese databases [21]. It showed that the CM group had a better improvement in VAS score than the pharmacotherapy group (WMD -1.73 points, 95% CI -2.12 to -1.35 , $I^2=0\%$). However, the details of interventions in both groups weren't specified. The results were not able to be interpreted in a meaningful way. This review aims to evaluate the efficacy and safety of oral CHM for PHN in randomised controlled trials (RCTs).

2. Methods

2.1. Data sources and search strategy

Nine electronic databases were searched from inception to February 2014, and an update search was conducted in March 2016. English databases included PubMed, which was used to search MEDLINE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Allied and Complementary Medicine Database (AMED) and Chinese databases included China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), the Chongqing VIP Chinese Scientific Journal database (CQVIP) and WanFang database. As PHN is a sequela of herpes zoster, search terms for both conditions were used. Search terms included neuralgia, postherpetic; PHN; post-herpetic pain; postherpetic pain; herpes zoster, varicellovirus, shingles, and variants. Search terms for Chinese herbal medicine included Traditional Chinese Medicine; Chinese Drugs, Plants; Plants, Medicinal; Herbs; and variants. Search terms for study designs included randomized controlled trial, controlled clinical trial, placebo, drug therapy, and variants. Both subject heading and keyword searches were conducted. Terms were also searched in the titles and abstracts. No restrictions were applied. The search was part of a comprehensive search for PHN with CM interventions; which included CHM; acupuncture; moxibustion; and other therapies of CM. This approach was aimed to ensure the largest sample of CHM was included.

2.2. Study selection criteria

The definition of PHN is still controversial. There have been many definitions of PHN reported in the literature, including pain at four weeks, six weeks, eight weeks, twelve weeks and six months after the resolution of the rash [3]. To date, no consensus definition of PHN has been reached [8]. Two clinical practice guidelines for HZ have proposed differing definitions, with the German Dermatology Society defining PHN as pain persisting for longer than four weeks [22], and Dworkin et al. [4] proposing PHN is pain persisting for at least 120 days after rash onset. The

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