Effectiveness of acupuncture therapy for postherpetic neuralgia: an umbrella review protocol

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ABSTRACT

Introduction Several systematic reviews and meta-analysis indicate that acupuncture and related therapies may be a valuable adjunctive technique to pharmacological interventions for pain management of postherpetic neuralgia (PHN). However, the robustness of the results of these studies has not been evaluated. The aim of this proposed umbrella review is to provide more reliable evidence of the effectiveness of acupuncture therapy for PHN based on medical references for healthcare decision makers.

Methods and analysis PubMed, EMBASE, The Cochrane Library, Web of Science, Chinese BioMedical Literature Database, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure and Wan fang Database will be used to retrieve reviews. The time of publication will be limited from inception to March 2021. Two reviewers will screen all retrieved articles independently to identify their eligibility and extract the data. The quality will be assessed independently by two trained reviewers using Assessment of Multiple Systematic Reviews-2 for methodological quality, Risk of Bias in Systematic Review for level of bias, Preferred Reporting Items for Systematic Reviews and Meta-Analysis for reporting quality and Grading of Recommendations Assessment, Development and Evaluation for the quality of evidence. Any disagreements will be settled by discussion or the involvement of a third reviewer.

Ethics and dissemination The protocol of this review does not require ethical approval because the research will be based on publicly available data. The findings will be disseminated through publication in peer-reviewed international journals or presentation in academic conference.


BACKGROUND

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster. It is usually defined as intense neuropathic pain that lasts more than 90 days after the acute rash is cured.\(^1\)\(^2\) PHN risk factors include age, sex, prodromal pain, severe acute pain, severe rash, ophthalmic involvement, severe immnosuppression, autoimmune conditions, asthma, diabetes and other suspect conditions.\(^3\)\(^4\) Approximately 5.8%-17.6% of patients with herpes zoster develop PHN.\(^5\)\(^6\)\(^7\) Especially the risk is sharply increased in elder patients, with risk of PHN in patients over 50 years old suffering from herpes zoster was found to be 14.7-24.7 times higher.\(^8\) Nearly half of the patients with herpes zoster over 70 years old develop PHN after the acute rash is cured.\(^9\) This trend is bound to increase year by year due to ageing population. A recent study found a relative risk of increasing PHN incidence per decade between 1.22 and 3.11.\(^4\) PHN not only severely impairs the quality of life of patients, but also increases the medical burden on individuals and society,\(^10\)\(^11\) and the medical costs associated with PHN are significantly higher than the costs associated with treatment of herpes zoster.\(^5\)\(^7\)\(^12\)\(^13\)

Unfortunately, the prevention and treatment of PHN is still in the preliminary stage. There is high-quality evidence that antiviral therapy given within 72 hours of the onset of acute herpes zoster does not significantly reduce the incidence of PHN.\(^14\) The overall vaccine effectiveness of the currently
approved zoster vaccine (live attenuated) for prevention of PHN is 64.8% (95% CI 61.3% to 68%), but immunosenescence cannot be avoided. Further, the cost-effectiveness analysis showed that the benefits of its application to the prevention of PHN in the 50-year-old population were limited. A herpes zoster recombinant subunit vaccine can diminish immunosenescence; however, more evidence is still needed for clinical application. At present, the strongly recommended treatment is still based on drug therapy. The commonly used drugs are tricyclic antidepressants, gabapentin and pregabalin. However, the effect of drug treatment is not satisfactory. Patients with moderate to severe PHN neuralgia who take gabapentin orally (1200–3600 mg/day, 4–12 weeks) have a response rate of at least 50% pain reduction that is only 14%–17% higher than that of placebo. Overestimation of treatment effects is common, at least by 10%. In addition, drugs often need to be taken for a long time, which is accompanied by a variety of adverse reactions, resulting in reduced patient compliance. In terms of non-drug therapy, interventional management is an emerging treatment for intractable neuralgia, but there is still insufficient evidence to prove the efficacy and safety of interventional therapy for PHN. Therefore, the prevention and treatment of PHN remains a formidable challenge at present.

Acupuncture has been widely used in pain relief for more than 2000 years in China. In the USA and Europe, acupuncture has been widely used in chronic pain management as an important component of the complementary and integrative medicine (CIM) since the National Institutes of Health (NIH) Consensus conference on acupuncture was held in 1998. CIM, formerly known as complementary medicine, is a combined therapeutic method that includes both Western-style medicine and complementary health approaches which most commonly includes the use of acupuncture, massage, chiropractic care and homeopathy. CIM offers a multidimensional treatment approach that can tackle the multidimensional nature of pain with fewer and less serious adverse effects. A large meta-analyses (MAs) based on individual patient data showed that the analgesic effect of acupuncture was not merely explained by placebo effect. The analgesic effect of acupuncture for patients with chronic pain was stable, lasting over 12 months, with only a small decrease of 15%. In addition, the mechanism of acupuncture analgesia has gradually been partially clarified. Acupuncture/electroacupuncture may induce a persistent analgesic effect by activating endogenous opioid peptides, serotonin, norepinephrine and other bioactive chemicals, decreasing spinal N-methyl-D-aspartate receptor subunit GluN1 phosphorylation, and reducing the release of proinflammatory cytokines, thereby inhibiting peripheral and central sensitisation. The purinergic signalling system may also be a considerable neurobiological basis of acupuncture analgesia. Moreover, advances in functional neuroimaging have found that acupuncture is involved in activating multiple brain regions associated with pain sensation, cognition and affection, revealing a multidimensional relationship between acupuncture and analgesia. Last but not least, the safety of properly performed acupuncture is proven.

Acupuncture is widely used in the treatment of PHN in China due to its positive analgesic effects. A growing number of systematic reviews and meta-analyses (SRs/MAs) have shown the effectiveness of acupuncture and relative treatments for PHN. For example, acupuncture and electroacupuncture were found to reduce pain intensity, relieve anxiety and improve quality of life in patients with PHN, and their efficacy may be better than that of pregabalin, carbamazepine, indomethacin, vitamin B1, vitamin B12 and mecobalamin. Moxibustion was found to be more effective in PHN than drug and physical therapy. Similarly, fire needle has been found to have obvious advantages compared with other therapies. Jiaji points combined with surrounding needling were found to have better efficacy than drugs in PHN. Corticosteroids injection in Jiaji acupoints may prevent or reduce the incidence of PHN in patients over 50 years old. However, some studies have pointed out that there is not enough evidence that acupuncture is superior to medication in improving pain intensity or quality of life in PHN. Among the various acupuncture treatments, there is no evidence that there is a difference in efficacy between moxibustion and acupuncture, or between electroacupuncture and manual acupuncture. In addition, the efficacy of acupuncture as adjuvant therapy for alleviating PHN is unclear. Such inconsistency in research conclusions adds to the confusion of clinical decision making. It is well known that SRs/MAs are important sources of the best evidence, and the results can be used to evaluate therapeutic efficacy and formulate clinical guidelines and standards. Nevertheless, only high-quality SRs/MAs can provide decision-making basis for clinicians, patients and other stakeholders. If the quality decreases due to research design defects and bias, it may be lessening the credibility of the evidence and misleading for clinical work. However, in fact, there are currently no overviews of the impact of acupuncture and related therapies for PHN. This overview will perform a formal assessment of the methodological and report quality of included SRs/MAs and provide the quality of evidence.

OBJECTIVES

Umbrella reviews aim to provide synthesised and appraised evidence to healthcare decision makers such as patients, physicians and policymakers. Specifically for this overview, we aim to answer the following research question: are acupuncture and related therapies effective for relieving pain associated with PHN? To achieve this objective, we will critically appraise the quality of the available full texts of SRs/MAs and will descriptively report the results of our findings in order to guide and add power to decision making.
METHODS

Patient and public involvement
It will not be appropriate or possible to involve patients or the public in this work as the overview is based on published SRs/MA.

Inclusion criteria for this overview

Types of studies
SRs and/or MA of randomised controlled trials (RCTs) examining the effectiveness of acupuncture and related therapies on PHN.

Types of participants
Participants with PHN will be included in this study without limitations related to age, sex, race or area. Considering that a large proportion of included studies are in Chinese, PHN is defined as pain persisting over 1 month after resolution of the rash according to the Chinese expert consensus on the diagnosis and treatment of PHN.49

Types of interventions
The main intervention of SRs is acupuncture. Acupuncture will not be restricted to certain types, such as manual acupuncture, electroacupuncture, moxibustion, bloodletting, cupping, fire needle, plum blossom needle, warm acupuncture, scalp acupuncture and auricular acupuncture, as well as combinations of these.

Types of comparators
The control groups of included SRs will be treated with sham-acupuncture, placebo/sham therapy, waiting list, medicine or non-pharmaceutical therapy.

Types of outcome measures

Main outcome(s)
Measuring pain severity using Numerical Rating Scale, Visual Analogue Scale, Verbal Rating Scale, McGill Pain Questionnaire, the Faces Pain Scale-Revised and any other scale for measuring pain.

Additional outcome(s)
Pain attack times, dosage of medication, pain-related emotional disorders measured using Hamilton Anxiety Scale, Hamilton Depression Scale, Sleep Quality Score or other validated scales. Safety of the acupuncture will be evaluated through adverse events and withdrawals for any reason.

Search methods for identification of studies

Database and search
The following electronic bibliographic databases will be searched from inception to 31 March 2021: PubMed, MEDLINE, EMBASE, The Cochrane Library, Chinese BioMedical Literature Database, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure and Wanfang Database. In addition, we will search grey literature in order to avoid missing eligible relevant reviews.

Restrictions
We will include SRs/MA that are published in English or Chinese and in full-text format. SRs/MA that are published as letter to the editor, abstract or conference poster will be excluded unless sufficient data could be acquired from the authors. The analysis will be conducted based on available data, and the potential impact of missing data will be discussed.

Search key terms
Terms of study-type-defining: systematic review(s), meta-analysis, meta analyses, data pooling(s) and clinical trial overview(s).

Terms of disease-defining: postherpetic neuralgia, PHN, herpes zoster and shingles.

Terms of intervention-defining: acupuncture, acupoint, needle, needling, electroacupuncture, electroacupuncture, pyonex, moxibustion, cupping, wet-cupping, pricking blood, bloodletting and blood-letting.

Search strategy
The search strategy with an example of PubMed database is shown in table 1.

Selection of SRs
After exclusion of duplicated articles by using NoteExpress (V.3.2.0; http://www.noteexpress.com/aegian/), two reviewers will independently screen eligibility articles based on the titles and abstracts according to the inclusive criteria. The full-text articles will be downloaded for further assessment if a judgement cannot be made based on the titles and abstracts. Search outcomes will be cross-checked by two reviewers. Discrepancies on articles will be solved by discussion or rechecked by a third reviewer.

Data extraction
We shall perform data extraction using Microsoft Excel (Microsoft, Redmont, Washington, USA). Two reviewers will independently extract the information of each included study into pre-designed data collection forms and then will cross check the data to correct enrolment errors. Information form includes authors, title, publication year, country, study type, registration platform, search strategy, sample size, intervention, comparator, quality evaluation method, outcomes and conclusion. Disagreements during this process will be resolved by discussion or the involvement of the third reviewer.

Quality of methodology assessment
Methodological quality is an important factor affecting the authenticity of SR; therefore, the Assessment of Multiple Systematic Reviews-2 (AMSTAR-2), the revised version of the original AMSTAR tool in 2017, will be used in this study to evaluate methodological quality of the included SRs/MA.50 51 The tool consists of 16 items covering the whole process of topic selection, design, registration, data extraction, data statistical analysis and discussion of the SRs. Among them,
Risk of bias (quality) assessment

Risk of Bias in Systematic Review (ROBIS) is a tool with fair reliability and good construct validity to assess the risk of bias in systematic reviews.\textsuperscript{32,33} The process of evaluating the risk of systematic review bias consists of three phases.

Phase 1 assesses relevance (optional). Phase 2 identifies four domains through which bias may be introduced in the process of SRs, including the inclusion criteria of the study, search and screening of the study, data extraction and quality evaluation, data synthesis and results presentation. Phase 3 judges the bias risk of the SRs. All signaling questions are rated applying the five possible answer categories ‘Yes’, ‘Probably Yes’, ‘Probably No’, ‘No’ and ‘No information’. The final judgement of overall risk of bias is rated as ‘low’, ‘unclear’ or ‘high’.

Quality of evidence assessment

Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a specialised tool for grading the quality of evidence for SRs.\textsuperscript{57} Evidence rating reasons include five downgrading factors and three upgrading factors. The downgrading factors are risk of bias, indirectness, inconsistency, imprecision and publication bias, while the upgrading factors were large effect, dose-response gradient and plausible confounding. Since only explanatory RCTs and practical RCTs will be included in this study, and the evidence starts at high quality, the downgrading factors will be used. The level of evidence is divided into four levels: ‘high’, ‘moderate’, ‘low’ or ‘very low’.

Data synthesis

Essential elements of available reviews contain the number of RCTs included in SRs/MAs, total sample size,
interventions, controls, outcome measures and adverse events. AMSTAR-2 will be used for methodological quality assessment, PRISMA will be used to assess report quality, ROBIS score for bias and GRADE for quality of evidence, which will be conducted in tabular form for each review. The quality of evidence will be detailed in tabular form. Data from individual studies are likely to be pooled multiple times across the reviews included in our overview. As a result, we will not conduct an MA of results. Rather, we will present a narrative synthesis of the findings from the included reviews, which will be reported as required by Preferred Reporting Items for Overview of Systematic Reviews Including Harms.

**DISCUSSION**

Overview is a research method that comprehensively collects and reviews the SRs/MA s related to a particular clinical problem, in order to obtain the synthesis evidence. It has the strength of higher level of evidence and better timeliness and feasibility in solving clinical problems. According to the 6S hierarchy of pre-appraised evidence, the transition from SRs/MA s to overviews is a necessary process for evidence summary, which is conducive to further improving the overall quality of systematic evaluation and the level of evidence from aspects of methodology and reporting standards.

With the rapid increasing publication of clinical studies on acupuncture and related therapies for PHN, the number of corresponding SRs/MA s also increases. However, the conclusions of these studies are inconsistent, which leads to confusion for clinical decision making. Therefore, it is crucial to conduct an overview to critically appraise the quality of these SRs/MA s to provide available reference for the clinical practice of acupuncture therapy for PHN, and to enhance the convenience and effectiveness of evidence search and utilisation.

Overview of SRs is a relatively new and evolving area of research, and therefore, a variety of methodological approaches exist. Qualitative description is usually used, but quantitative analysis, such as MA or network MA, can also be used to carry out quantitative synthesis of the included data. Considering that data from individual studies may be aggregated multiple times in our study, we will not conduct an MA of the results. Instead, we will critically evaluate the quality of the SRs/MA s in terms of methodological quality, reporting quality and risk bias.

In conclusion, the quality of evidence on acupuncture efficacy as adjuvant therapy for alleviating PHN remains unclear. This umbrella review will provide comprehensive evidence on whether acupuncture and relative therapies should be recommended to patients with PHN s in clinical practice.

**ETHICS AND DISSEMINATION**

Considering that there will be no violation of privacy, as the available data will be extracted from published SRs/MA s, ethical approval will be not required. We intend to disseminate the results by publication in a peer-reviewed international journal or presentation in academic conference.

**Acknowledgements**

The authors thank Profesors Li Ying and Dr Shi Yun-zhou from Chengdu University of Traditional Chinese Medicine for their suggestions on the design of this review. Grateful thanks are due to Editage (www.editage.cn) for its linguistic assistance during the preparation of this manuscript.

**Contributors**

YZ and D-YL are joint first authors. YZ and D-YL designed the study and YZ submitted the registration on PROSPERO. GW and Z-WZ developed the draft search strategy according to the registration. YZ drafted the manuscript, and JZ revised the language. Z-YW approved the final version of the manuscript. All authors have read and approved the final manuscript. YZ and Z-YW are the study guarantors.

**Funding**

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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