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Acupuncture for post-herpetic neuralgia: a systematic review protocol

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Acupuncture for post-herpetic neuralgia: a systematic review protocol

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Running Title: Acupuncture for post-herpetic neuralgia: a protocol

Keywords: acupuncture, postherpetic neuralgia, systematic review, protocol, randomized controlled trials

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Abstract

Background: Post-herpetic neuralgia (PHN) is a syndrome characterized by pain persisting more than 3 months following the resolution of herpes zoster (HZ). PHN frequently resolves spontaneously over time and the efficacy of the treatments for PHN is evaluated unclearly. Acupuncture has a history of over 2000 years in both the prevention and treatment of diseases. Preliminary searches for recent 5 years have revealed more than 137 studies of acupuncture for treating PHN, and benefit of the treatment group was reported between 84.1% and 97.5%. The objective of this systematic review is to assess the efficacy and safety of acupuncture for PHN in pain-relieving and pain-removing.

Methods/design: This systematic review will electronically search multiple databases and hand search a list of medical journals, and will contact authors to identify studies. Two reviewers will independently screen reports and extract data. Primary outcome is pain intensity measured by Visual Analogue Scale (VAS), etc., and secondary outcomes are global impression, quality of life, safety measured by incidence and severity of adverse effects and costs. Meta-analysis will be conducted by pooling risk ratio for dichotomous data, standardized or weighted mean difference for continuous data.

Conclusion: This review will accumulate the current evidence on the efficacy and safety of acupuncture for PHN. Furthermore, it will benefit policy makers, patients, and clinicians seeking innovative and effective ways to achieve pain relief and removal for PHN.

Dissemination: This study will be disseminated through peer-review publication or conference presentation.

Trial registration: PROSPERO registration number: CRD42014009555

Keywords: acupuncture, postherpetic neuralgia, systematic review, protocol, randomized controlled trials

STRENGTHS AND LIMITATIONS OF THIS STUDY

This systematic review will be the first one to assess the efficacy and safety of acupuncture for PHN. And it will provide a high-quality synthesis of current evidence for policy makers, patients, and clinicians seeking innovative and effective ways to treat PHN.

The ability to generate conclusions of high confidence in this study may be limited, due to the heterogeneity in the forms of acupuncture therapies and the qualities of methodology, and the impossibility of searching in all the electronic databases or other data sources.

Background

Post-herpetic neuralgia (PHN) is a syndrome characterized by pain persisting more than 3 months following the resolution of herpes zoster (HZ) ^[1-4]. In addition, the clinical manifestations include allodynia, dysesthesia and pruritus along the distribution of the involved dermatome. The incidence of PHN is 4/1000 per year, which further increases to 12/1000 among people over 80 years old ^[5]. The relevant risk factors for PHN include old age, female gender, greater severity of acute pain, greater rash severity, the degree of sensory impairment, psychological distress, a painful prodrome, diabetes mellitus, nutritional deficiencies and diminished cell-mediated immunity ^[6-10]. However, the most relevant risk factor is old age ^[11-12]. It is uncommon for people under 50 years old, but approximately 83% of PHN occurring above ^[13].

Due to the persisting or intermittent spontaneous pain, post-herpetic neuralgia brings a serious impact on the patients' daily activities (e.g. dressing, bathing, sleep), quality of life, general health, psychological health (e.g. depression and difficulty with concentration), and social and economic well-being ^[14-15]. Though the pathophysiology of PHN is poorly understood, postmortem studies in patients with PHN have found demyelination and axonal loss both peripheral nerves and sensory roots ^[16].

Because PHN frequently resolves spontaneously over time and the efficacy of the treatments for PHN is evaluated unclearly ^[17-18], pain reduction may be incorrectly attributed to current treatments for PHN. There are conventional treatments for PHN, such as tricyclic antidepressants (TCAs), antiepileptics, opioids, tramadol, lidocaine and capsaicin, which are probably effective to relieve some of the pain for a period of time. However, approximately 50% of patients may not obtain satisfactory analgesia despite treatments with these medications ^[4]. Moreover, being the first-line treatment suggested worldwide for PHN, TCAs and antiepileptics (gabapentin and pregabalin) still bring a high incidence of adverse events (AEs), including sedation, xerostomia, confusion, dysrhythmia, weight gain, dizziness, somnolence, fatigue and ataxia ^[18-21].

Acupuncture, which has a history of more than 2000 years in both the prevention and treatment of diseases, plays an important role in Traditional Chinese Medicine (TCM). Kinds of acupuncture methods such as fire needling, electro-acupuncture, surrounding needling, pyonex, pricking blood and cupping are in use for the treatment of PHN in hospitals in China. Preliminary searches for recent 5 years have revealed more than 137 studies of acupuncture for treating PHN. And benefit of the treatment group was reported between 84.1% and 97.5 % ^[22-24]. The clinical trials indicate that acupuncture could reduce pain and discomfort among most patients and remove pain and discomfort among some patients.

However, the efficacy and safety of acupuncture for PHN have not been systematically reviewed. Thus, this systematic review is conducted to assess the efficacy and safety of acupuncture for PHN in pain-relieving and pain-removing.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Type of studies

Randomized controlled trials (RCTs) will be included without restriction of language or publication type. Moreover, the trials using open label, single blind and double blind design will all be included, while cross-over designs and quasi- RCTs will be excluded.

Type of participants

The participants, who had been diagnosed as post-herpetic neuralgia defined as pain persisting over 3 months after resolution of the rash, will be all focused on. No restrictions on age, gender or race.

Types of interventions

Any form of acupuncture therapy used in experimental group will be included, involving acupuncture, electro-acupuncture, elongated needle, three-edged needle, fire needling, auricular acupuncture, pyonex, moxibustion, pricking blood, and cupping.

The control interventions with no treatment control, sham acupuncture control (non-point acupuncture, minimal acupuncture), placebo control and drug therapy control will be included.

Studies with the following comparisons will be included:

1. Acupuncture versus another therapy.
2. Acupuncture with another therapy versus the same other therapy.

Types of outcome measures*Primary outcomes*

1. Pain intensity as measured by Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), the Faces Pain Scale-Revised (FPS-R), etc.

Secondary outcomes

1. Global impression
2. Quality of life
3. Safety as measured by incidence and severity of adverse effects
4. Costs

Search methods for identification of studies

A search strategy will be designed and conducted according to the guidance of the Cochrane handbook ^[25].

Electronic searches

We will search the following databases:

1. the Cochrane Skin Group Trials Register(the inception to 2014.1)
2. MEDLINE(the inception to 2014.1)
3. EMBASE(the inception to 2014.1)
4. the Cochrane Central Register of Controlled Trials (CENTRAL) (the inception to 2014.1)
5. Chinese Biomedical Literature Database (CBM) (the inception to 2014.1)

6. Chinese Medical Current Content (CMCC) (the inception to 2014.1)
7. China National Knowledge Infrastructure (CNKI) (the inception to 2014.1)

This review will use the following search terms: postherpetic neuralgia, PHN, herpes zoster, shingles and acupuncture, electro-acupuncture, elongated needle, fire needling, auricular acupuncture, pyonex, moxibustion, pricking blood, three-edged needle, cupping. This study will adapt this strategy to search all the above databases.

There will be no restriction on language or publication type. The search strategy for MEDLINE can be found in Appendix 1.

Searching other resources

Hand search a list of medical journals in university libraries, such as Chinese Acupuncture & Moxibustion(1981-2014.1), Journal of Clinical Acupuncture & Moxibustion(1985-2014.1), Shanghai Journal of Acupuncture & Moxibustion(1982-2014.1) and Acupuncture Research(1976-2014.1).

Data collection and analysis

Selection of studies

A procedure for screening will be discussed and developed before the start of selection. Both the outputs searched electronically and the studies obtained from other sources will be cited in a database created by NoteExpress software. Two reviewers (LW and ZJ) will independently screen all the titles and abstracts of studies to find out the duplicates, as well as to review the studies and decide whether they will be included according to the predefined inclusion criteria. If there are studies that could not be clearly included based on both titles and abstracts, full copies will be screened. Once any disagreement occurs, it will be resolved through discussion and resolved by reaching a consensus among the two reviewers (LW and ZJ), or consult of a third arbitrator (LZS). In addition, the kappa value will be used to calculate the consistency evaluation between reviewers.

Data extraction and management

Data extractors (LW and ZJ) will independently extract data from the included trials by using a piloted data extraction form which is discussed and developed by all the reviewers. The extracted data will include data for trails, participants, interventions, outcomes and miscellaneous items such as funding sources and ethical approval. Any disagreement in data extraction will be resolved by discussion or consult of a third arbitrator (LZS). If data presented in studies is unclear, missing, or presented in a form that is either un-extractable or difficult to reliably extract, the authors of the study will be contacted for clarification.

Assessment of risk of bias in included studies

According to the Cochrane Handbook of Systematic Reviews of Interventions^[25], the reviewers will firstly access six domains of each trial (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'), then summarize the assessments, and at last categorize the included trials into 3 levels of bias: low, unclear and high

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3 risk of bias. The risk of bias will be assessed independently. Any disagreements will be resolved
4 by discussion or consult of a third arbitrator.
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7 **Measures of treatment effect**

8 Where continuous scales of measurement are used to assess the effects of treatment, the
9 weighted mean difference (WMD) with 95% confidence intervals (CI) will be used, or the
10 standardized mean difference (SMD) with 95%CI if different measurement tools and units have
11 been used. For dichotomous outcomes results will be expressed as the relative risk (RR) with
12 95%CI.
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15 **Unit of analysis issues**

16 Studies with multiple intervention groups will be included. Each intervention group will be
17 compared to the single control group.
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20 **Dealing with missing data**

21 The authors of the included studies will be contacted to get further information if there are any
22 missing or insufficient data from the trials. And relevant data obtained in this manner will be
23 included in the review. The intent-to-treat (ITT) principle (available case analysis and full
24 intent-to-treat analysis) will be applied for statistical analysis, without getting the missing data.
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28 **Assessment of heterogeneity**

29 Heterogeneity will be investigated by the I^2 statistic (I^2 to or more than 50% was considered
30 indicative of heterogeneity) and the chi-squared (χ^2 , or Chi^2) test ^[25]. The Chi^2 test will use an
31 alpha of 0.1 for statistical significance and the P-value to be less than 0.1 will be accepted as
32 heterogeneity.
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36 **Assessment of reporting biases**

37 Funnel plots will be used to assess reporting biases, if ten or more studies are included in a
38 meta-analysis. Such a funnel plot asymmetry could be caused by publication or related biases, or
39 by systematic differences between small and large studies. If a relationship is identified, the
40 clinical diversity of the studies will be further examined as a possible explanation and described
41 in the text. However, because graphical evaluation can be subjective, Egger's method will also be
42 used to assess the reporting biases ^[26].
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46 **Data synthesis**

47 The Revman 5.1 software will be used to conduct Meta analysis and calculate the RR with 95%CI
48 for the dichotomous data, the WMD or the SMD with 95%CI for continuous data during synthesis.
49 If the same outcome measurement tool and unit is used, the WMD with 95%CI will be calculated,
50 or SMD with 95%CI instead. If the included studies exist heterogeneity, the P value is less than
51 0.1, the RR, the WMD, or the SMD will be calculated by the random effects model. Otherwise, it
52 will be calculated by a fixed effect model.
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56 **Subgroup analysis**

57 Subgroup analysis will be performed based on different controls, interventions, durations of
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3 treatment, and outcome measures. Adverse effects will be tabulated and assessed with
4 descriptive techniques.
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7 **Sensitivity analysis**

8 For the sensitivity analysis, the meta-analysis will repeat, substituting decisions alternatively to
9 test the robustness of the primary decisions of the review process^[27]. The decision nodes are
10 principally the methodological qualities, the sample size and the option of using missing data
11 (available case analysis and full intent-to-treat analysis).
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14 **Discussion**

15 PHN brings a significant adverse impact on patients' daily activities, quality of life, general health,
16 psychological health, and social and economic well-being. Acupuncture therapy is a suggested
17 intervention in China that may have value to treat PHN, but no high-quality synthesis of the
18 evidence exists.
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21 This study might have kind of limitations that may limit its ability to generate conclusions based
22 on high confidence. Specifically, there may be significant heterogeneity in the forms of
23 acupuncture therapies used and the qualities of methodology. There will also likely be
24 differences in outcomes measured and tools used. Inherent uncertainty exists by pooling this
25 data within constructed domains.
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28 This review has not searched studies in more electronic databases or a grey list, which could limit
29 the broad search of RCTs to generate the findings.
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32 **Conclusion**

33 This systematic review will accumulate the current evidence on the efficacy and safety of
34 acupuncture for PHN. And it will benefit policy makers, patients, and clinicians seeking innovative
35 and effective ways to achieve pain relief and removal for PHN.
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38 **Authors' contributions:** Wang LI and Zhishun LIU contributed to the conception of the study. The manuscript of
39 the protocol was drafted by Wang LI, and was revised by Weina PENG. The search strategy was developed by all
40 authors and run by Wang LI and Jing ZHOU, who will also independently screen the potential studies, extract data
41 of included studies, assess the risk of bias and finish data synthesis. Zhishun LIU will arbitrate the disagreements
42 and ensure that no errors occur during the study. All authors approved for the publication of the protocol.
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46 **Funding statement:** This research received no specific grant from any funding agency in the public, commercial
47 or not-for-profit sectors.
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50 **Competing interests:** No competing interests exist.
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53 **Ethical approval:** This research does not need ethical approval because data we used will not be linked to
54 individual data and privacy.
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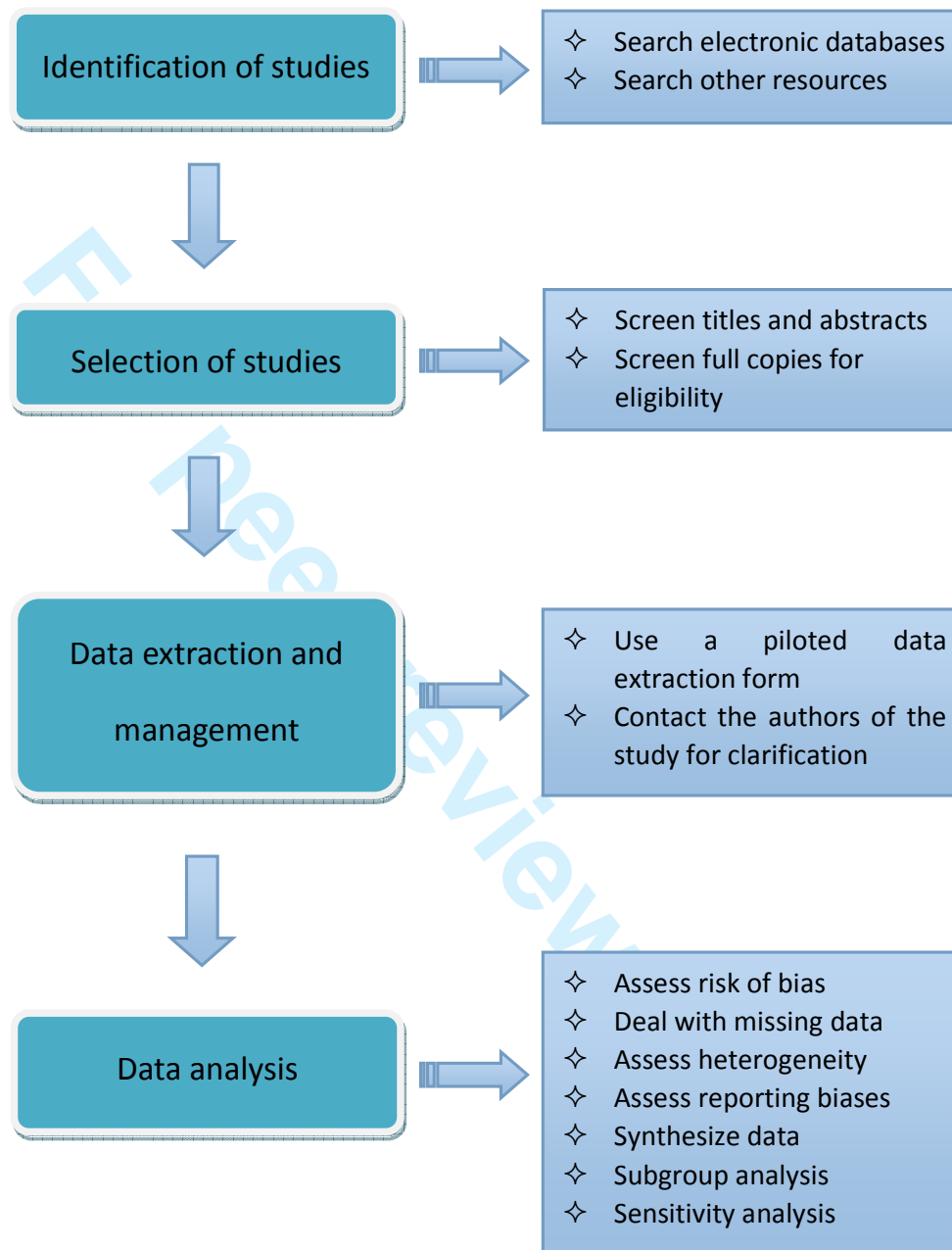
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Appendices**Appendix 1. OVID MEDLINE search strategy**

1. randomized controlled trial. pt.
2. controlled clinical trial. pt.
3. randomized. ti, ab.
4. randomly. ti, ab.
5. trial. ti, ab.
6. groups. ti, ab.
7. or/1-6
8. exp acupuncture therapy, or acupuncture
9. acupressure. ti, ab.
10. (acupoint \$ or electroacupuncture or electro-acupuncture). ti, ab.
11. elongated needle \$. ti, ab.
12. (three edged needl \$ or three-edged needl). ti, ab.
13. (fire needling or warming needl). ti, ab.
14. auricular acupuncture. ti, ab.
15. pyonex. ti, ab.
16. moxibustion. ti, ab.
17. (pricking blood or bloodletting or blood-letting). ti, ab..
18. cupping. ti, ab.
19. Or/8-18
20. exp postherpetic neuralgia, or post-herpetic neuralgia
21. PHN. ti, ab.
22. herpes zoster. ti, ab.
23. shingles. ti, ab.
24. (neuralgia or postherpetic) . ti, ab.
25. herpes zoster. ti, ab.
26. Or/20-25
27. 7 and 19 and 26

This search strategy will be suitable for other electronic databases.

Appendix 2. Flow chart



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Secondary Subject Heading:	Evidence based practice, Medical publishing and peer review, Dermatology
Keywords:	DERMATOLOGY, COMPLEMENTARY MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neurological pain < NEUROLOGY, PAIN MANAGEMENT

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15 Running Title: Acupuncture for post-herpetic neuralgia: a protocol
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18 Keywords: acupuncture, postherpetic neuralgia, systematic review, protocol
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22 Word Count: 1880
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Abstract

Introduction: Post-herpetic neuralgia (PHN) is one of the most common complications following herpes zoster (HZ). The clinical trials indicate that acupuncture could reduce pain and discomfort among patients with PHN. This protocol aims to describe how to accumulate the current evidence on the efficacy and safety of acupuncture for treating PHN.

Methods and Analysis: This systematic review will electronically search multiple databases including the Cochrane Skin Group Trials Register, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), Chinese Medical Current Content (CMCC), and China National Knowledge Infrastructure (CNKI), and will hand search a list of medical journals as a supplement. Any clinical randomized controlled trials (RCTs) related to acupuncture for treating PHN will be included. Outcomes will include pain intensity, global impression, quality of life, safety and costs. Two reviewers will independently screen the titles, the abstracts or even full texts, and extract data, assess study quality. Meta-analysis will be conducted by pooling risk ratio for dichotomous data, standardized or weighted mean difference for continuous data.

Ethics and dissemination: This systematic review does not need ethical approval because there's no data used in our study linked to individual patient data. And the findings will be disseminated through peer-review publication or conference presentation.

Trial registration: PROSPERO registration number: CRD42014009555

STRENGTHS AND LIMITATIONS OF THIS STUDY

This systematic review will be the potent one to assess the efficacy and safety of acupuncture for PHN. And it will provide a high-quality synthesis of current evidence for policy makers, patients, and clinicians seeking innovative and effective ways to treat PHN.

The ability to generate conclusions of high confidence in this study may be limited, due to the heterogeneity in the forms of acupuncture therapies and the qualities of methodology, and the impossibility of searching in all the electronic databases or other data sources.

INTRODUCTION

Post-herpetic neuralgia (PHN) is a syndrome characterized by pain persisting more than 3 months following the resolution of herpes zoster (HZ) ^[1-4]. In addition, the clinical manifestations include allodynia, dysesthesia and pruritus along the distribution of the involved dermatome. The incidence of PHN is 4/1000 per year, which further increases to 12/1000 among people over 80 years old ^[5]. The relevant risk factors for PHN include old age, female gender, greater severity of acute pain, greater rash severity, the degree of sensory impairment, psychological distress, a painful prodrome, diabetes mellitus, nutritional deficiencies and diminished cell-mediated immunity ^[6-10]. However, the most relevant risk factor is old age ^[11-12]. It is uncommon for people under 50 years old, but approximately 83% of PHN occurring above ^[13].

Due to the persisting or intermittent spontaneous pain, post-herpetic neuralgia brings a serious impact on the patients' daily activities (e.g. dressing, bathing, sleep), quality of life, general health, psychological health (e.g. depression and difficulty with concentration), and social and economic well-being ^[14-15]. Though the pathophysiology of PHN is poorly understood, postmortem studies in patients with PHN have found demyelination and axonal loss in both peripheral nerves and sensory roots ^[16].

Because PHN frequently resolves spontaneously over time and the evaluation is unclear for the efficacy of the treatments ^[17-18], pain reduction may be incorrectly attributed to current treatments for PHN. There are conventional treatments for PHN, such as tricyclic antidepressants (TCAs), antiepileptics, opioids, tramadol, lidocaine and capsaicin, which are probably effective to relieve some of the pain for a period of time. However, approximately 50% of patients still may not obtain satisfactory analgesia despite of treatments with these medications ^[4]. Moreover, being the first-line treatment suggested worldwide for PHN, TCAs and antiepileptics (gabapentin and pregabalin) still bring a high incidence of adverse events (AEs), including sedation, xerostomia, confusion, dysrhythmia, weight gain, dizziness, somnolence, fatigue and ataxia ^[18-21].

Acupuncture, which has a history of more than 2000 years in both the prevention and treatment of diseases, plays an important role in Traditional Chinese Medicine (TCM). Kinds of acupuncture methods such as fire needling, electro-acupuncture, surrounding needling, pyonex, pricking blood and cupping are in use for the treatment of PHN in hospitals in China. In recent 5 years, acupuncture for treating PHN has been used in more than 137 studies. And benefit of the treatment group was reported between 84.1% and 97.5 % ^[22-24]. The clinical trials indicate that acupuncture could reduce pain and discomfort among most patients and remove pain and discomfort among some patients.

However, the efficacy and safety of acupuncture for PHN are lack of high-quality synthesis of current evidence. Thus, this systematic review is conducted to assess the efficacy and safety of acupuncture for PHN in pain-relieving and pain-removing.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Type of studies

Randomized controlled trials (RCTs) will be included without restriction of language or publication type. Moreover, the trials using open label, single blind and double blind design will all be included, while cross-over designs and quasi- RCTs will be excluded.

Type of participants

The participants, who had been diagnosed as post-herpetic neuralgia defined as pain persisting over 3 months after resolution of the rash, will be all focused on. No restrictions on age, gender or race.

Types of interventions

Any form of acupuncture therapy used in experimental group will be included, involving acupuncture, electro-acupuncture, elongated needle, three-edged needle, fire needling, auricular acupuncture, pyonex, moxibustion, pricking blood, and cupping.

The control interventions with no treatment control, sham acupuncture control (non-point acupuncture, minimal acupuncture), placebo control and drug therapy control will be included.

Studies with the following comparisons will be included:

1. Acupuncture versus another therapy.
2. Acupuncture with another therapy versus the same other therapy.
3. Acupuncture versus no active intervention.
4. Acupuncture versus sham acupuncture.

Types of outcome measures

Primary outcomes

Pain intensity

Studies which applied scales such as Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), the Faces Pain Scale-Revised (FPS-R), etc. that were used to measure the intensity of pain will be included.

Secondary outcomes

1. Global impression (the proportion of participants whose symptoms improved after treatments)
2. Quality of life
3. Safety as measured by incidence and severity of adverse effects
4. Costs

Search methods for identification of studies

A search strategy will be designed and conducted according to the guidance of the Cochrane handbook ^[25].

Electronic searches

We will search the following databases:

1. the Cochrane Skin Group Trials Register(the inception to 2014.1)
2. MEDLINE(the inception to 2014.1)
3. EMBASE(the inception to 2014.1)
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5. Chinese Biomedical Literature Database (CBM) (the inception to 2014.1)
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7. China National Knowledge Infrastructure (CNKI) (the inception to 2014.1)

This review will use the following search terms: postherpetic neuralgia, PHN, herpes zoster, shingles and acupuncture, electro-acupuncture, elongated needle, fire needling, auricular acupuncture, pyonex, moxibustion, pricking blood, three-edged needle, cupping. This study will adapt this strategy to search all the above databases.

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A list of medical journals in university libraries will be searched as a supplement, such as Chinese Acupuncture & Moxibustion(1981-2014.1), Journal of Clinical Acupuncture & Moxibustion(1985-2014.1), Shanghai Journal of Acupuncture& Moxibustion(1982-2014.1) and Acupuncture Research(1976-2014.1).

Data collection and analysis

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3 studies is unclear, missing, or presented in a form that is either un-extractable or difficult to
4 reliably extract, the authors of the study will be contacted for clarification.
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7 **Assessment of risk of bias in included studies**

8 According to the Cochrane Handbook of Systematic Reviews of Interventions ^[25], the reviewers
9 will firstly access six domains of each trial (sequence generation, allocation concealment, blinding,
10 incomplete outcome data, selective outcome reporting and 'other issues'), then summarize the
11 assessments, and at last categorize the included trials into 3 levels of bias: low, unclear and high
12 risk of bias. The risk of bias will be assessed independently. Any disagreements will be resolved
13 by discussion or consult of a third arbitrator.
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16 **Measures of treatment effect**

17 Where continuous scales of measurement are used to assess the effects of treatment, the
18 weighted mean difference (WMD) with 95% confidence intervals (CI) will be used, or the
19 standardized mean difference (SMD) with 95%CI if different measurement tools and units have
20 been used. For dichotomous outcomes results will be expressed as the relative risk (RR) with
21 95%CI.
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24 **Unit of analysis issues**

25 Studies with multiple intervention groups will be included. Each intervention group will be
26 compared to the single control group.
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29 **Dealing with missing data**

30 The authors of the included studies will be contacted to get further information if there are any
31 missing or insufficient data from the trials. And relevant data obtained in this manner will be
32 included in the review. The intent-to-treat (ITT) principle (available case analysis and full
33 intent-to-treat analysis) will be applied for statistical analysis, without getting the missing data.
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37 **Assessment of heterogeneity**

38 Heterogeneity will be investigated by the I^2 statistic (I^2 to or more than 50% was considered
39 indicative of heterogeneity) and the chi-squared (χ^2 , or Chi^2) test ^[25]. The Chi^2 test will use an
40 alpha of 0.1 for statistical significance and the P-value to be less than 0.1 will be accepted as
41 heterogeneity.
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45 **Assessment of reporting biases**

46 Funnel plots will be used to assess reporting biases, if ten or more studies are included in a
47 meta-analysis. Such a funnel plot asymmetry could be caused by publication or related biases, or
48 by systematic differences between small and large studies. If a relationship is identified, the
49 clinical diversity of the studies will be further examined as a possible explanation and described
50 in the text. However, because graphical evaluation can be subjective, Egger's method will also be
51 used to assess the reporting biases ^[26].
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55 **Data synthesis**

56 The Revman 5.1 software will be used to conduct Meta analysis and calculate the RR with 95%CI
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3 for the dichotomous data, the WMD or the SMD with 95%CI for continuous data during synthesis.
4 If the same outcome measurement tool and unit is used, the WMD with 95%CI will be calculated,
5 or SMD with 95%CI instead. If the included studies exist heterogeneity, the P value is less than
6 0.1, the RR, the WMD, or the SMD will be calculated by the random effects model. Otherwise, it
7 will be calculated by a fixed effect model.
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10 **Subgroup analysis**

11 Subgroup analysis will be performed based on different controls, interventions, durations of
12 treatment, and outcome measures. Adverse effects will be tabulated and assessed with
13 descriptive techniques.
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16 **Sensitivity analysis**

17 For the sensitivity analysis, the meta-analysis will repeat, substituting decisions alternatively to
18 test the robustness of the primary decisions of the review process^[27]. The decision nodes are
19 principally the methodological qualities, the sample size and the option of using missing data
20 (available case analysis and full intent-to-treat analysis).
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24 **DISCUSSION**

25 PHN brings a significant adverse impact on patients' daily activities, quality of life, general health,
26 psychological health, and social and economic well-being. Acupuncture therapy is a suggested
27 intervention in China that may have value to treat PHN, but no high-quality synthesis of the
28 evidence exists. Thus, a high-quality systematic review is needed and the process of performing
29 this study can be found in figure 1 which will be separated into four parts: identification,
30 selection, data extraction and management, and data analysis.
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34 This study might have kind of limitations that may limit its ability to generate conclusions based
35 on high confidence. Specifically, there may be significant heterogeneity in the forms of
36 acupuncture therapies used and the qualities of methodology. There will also likely be
37 differences in outcomes measured and tools used. Inherent uncertainty exists by pooling this
38 data within constructed domains.
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42 This review has not searched studies in more electronic databases or a grey list, which could limit
43 the broad search of RCTs to generate the findings.
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4 **Authors' contributions:** Wang LI and Zhishun LIU contributed to the conception of the study. The manuscript of
5 the protocol was drafted by Wang LI, and was revised by Weina PENG. The search strategy was developed by all
6 authors and run by Wang LI and Jing ZHOU, who will also independently screen the potential studies, extract data
7 of included studies, assess the risk of bias and finish data synthesis. Zhishun LIU will arbitrate the disagreements
8 and ensure that no errors occur during the study. All authors approved for the publication of the protocol.
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12 **Funding statement:** This research received no specific grant from any funding agency in the public, commercial
13 or not-for-profit sectors.
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17 **Competing interests:** No competing interests exist.
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19 **Figure1. Flow chart of the systematic review**
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Acupuncture for post-herpetic neuralgia: a systematic review protocol

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2 Beijing University of Traditional Chinese Medicine, Beijing (100029), China.

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Running Title: Acupuncture for post-herpetic neuralgia: a protocol

Keywords: acupuncture, postherpetic neuralgia, systematic review, protocol, ~~randomized controlled trials~~

Word Count: 1880

Abstract

Background: Post-herpetic neuralgia (PHN) is a syndrome characterized by pain persisting more than 3 months following the resolution of herpes zoster (HZ). PHN frequently resolves spontaneously over time and the efficacy of the treatments for PHN is evaluated unclearly. Acupuncture has a history of over 2000 years in both the prevention and treatment of diseases. In recent 5 years, acupuncture for treating PHN has been used in more than 137 studies, and benefit of the treatment group was reported between 84.1% and 97.5%. The objective of this systematic review is to assess the efficacy and safety of acupuncture for PHN in pain relieving and pain removing. **Introduction:** Post-herpetic neuralgia (PHN) is one of the most common complications following herpes zoster (HZ). The clinical trials indicate that acupuncture could reduce pain and discomfort among patients with PHN. This protocol aims to describe how to accumulate the current evidence on the efficacy and safety of acupuncture for treating PHN. **Methods/design and Analysis:** This systematic review will electronically search multiple databases and hand search a list of medical journals, and will contact authors to identify unclear information. Two reviewers will independently screen the titles, the abstracts or even full texts and extract data. Primary outcome is pain intensity measured by Visual Analogue Scale (VAS), etc., and secondary outcomes are global impression, quality of life, safety measured by incidence and severity of adverse effects and costs. Meta-analysis will be conducted by pooling risk ratio for dichotomous data, standardized or weighted mean difference for continuous data. This systematic review will electronically search multiple databases including the Cochrane Skin Group Trials Register, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), Chinese Medical Current Content (CMCC), and China National Knowledge Infrastructure (CNKI), and will hand search a list of medical journals as a supplement. Any clinical randomized controlled trails (RCTs) related to acupuncture for treating PHN will be included. Outcomes will include pain intensity, global impression, quality of life, safety and costs. Two reviewers will independently screen the titles, the abstracts or even full texts, and extract data, access study quality. Meta-analysis will be conducted by pooling risk ratio for dichotomous data, standardized or weighted mean difference for continuous data. **Conclusion:** This review will accumulate the current evidence on the efficacy and safety of

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6 acupuncture for PHN. Furthermore, it will benefit policy makers, patients, and clinicians seeking
7 innovative and effective ways to achieve pain relief and removal for PHN.

8 **Ethics and Dissemination:** [This systematic review does not need ethical approval because](#)
9 [there's no data used in our study linked to individual patient data. And ~~This study~~the findings](#) will
10 be disseminated through peer-review publication or conference presentation.

11 **Trial registration:** PROSPERO registration number: CRD42014009555

12 **Keywords:** [acupuncture, postherpetic neuralgia, systematic review, protocol, randomized](#)
13 [controlled trials](#)

14 15 16 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

17 This systematic review will be the [first](#)potent one to assess the efficacy and safety of
18 acupuncture for PHN. And it will provide a high-quality synthesis of current evidence for policy
19 makers, patients, and clinicians seeking innovative and effective ways to treat PHN.

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21 The ability to generate conclusions of high confidence in this study may be limited,
22 due to the heterogeneity in the forms of acupuncture therapies and the qualities of methodology,
23 and the impossibility of searching in all the electronic databases or other data sources.

24 25 26 27 **Background**INTRODUCTION

28 Post-herpetic neuralgia (PHN) is a syndrome characterized by pain persisting more than 3
29 months following the resolution of herpes zoster (HZ) ^[1-4]. In addition, the clinical
30 [manifestations](#)manifestations include allodynia, dysesthesia and pruritus along the distribution of
31 the involved dermatome. The incidence of PHN is 4/1000 per year, which further increases to
32 12/1000 among people over 80 years old ^[5]. The relevant risk factors for PHN include old age,
33 female gender, greater severity of acute pain, greater rash severity, the degree of sensory
34 impairment, psychological distress, a painful prodrome, diabetes mellitus, nutritional deficiencies
35 and diminished cell-mediated immunity ^[6-10]. However, the most relevant risk factor is old age
36 ^[11-12]. It is uncommon for people under 50 years old, but approximately 83% of PHN occurring
37 above ^[13].

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39 Due to the persisting or intermittent spontaneous pain, post-herpetic neuralgia brings a serious
40 impact on the patients' daily activities (e.g. dressing, bathing, sleep), quality of life, general
41 health, psychological health (e.g. depression and difficulty with concentration), and social and
42 economic well-being ^[14-15]. Though the pathophysiology of PHN is poorly understood,
43 postmortem studies in patients with PHN have found demyelination and axonal loss [in](#) both
44 peripheral nerves and sensory roots ^[16].

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46 Because PHN frequently resolves spontaneously over time and [the evaluation is unclear for](#) the
47 efficacy of the treatments [for PHN is evaluated unclearly](#) ^[17-18], pain reduction may be incorrectly
48 attributed to current treatments for PHN. There are conventional treatments for PHN, such as
49 tricyclic antidepressants (TCAs), antiepileptics, opioids, tramadol, lidocaine and capsaicin, which
50 are probably effective to relieve some of the pain for a period of time. However, approximately
51 50% of patients [still](#) may not obtain satisfactory analgesia despite [of](#) treatments with these
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6 medications^[4]. Moreover, being the first-line treatment suggested worldwide for PHN, TCAs and
7 antiepileptics (gabapentin and pregabalin) still bring a high incidence of adverse events (AEs),
8 including sedation, xerostomia, confusion, dysrhythmia, weight gain, dizziness, somnolence,
9 fatigue and ataxia^[18-21].

11
12 Acupuncture, which has a history of more than 2000 years in both the prevention and treatment
13 of diseases, plays an important role in Traditional Chinese Medicine (TCM). Kinds of acupuncture
14 methods such as fire needling, electro-acupuncture, surrounding needling, pyonex, pricking
15 blood and cupping are in use for the treatment of PHN in hospitals in China. [In recent 5 years,](#)
16 [acupuncture for treating PHN has been used in more than 137 studies.](#) ~~Preliminary searches for~~
17 ~~recent 5 years have revealed more than 137 studies of acupuncture for treating PHN.~~ And benefit
18 of the treatment group was reported between 84.1% and 97.5%^[22-24]. The clinical trials indicate
19 that acupuncture could reduce pain and discomfort among most patients and remove pain and
20 discomfort among some patients.
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23 However, the efficacy and safety of acupuncture for PHN ~~have not been systematically~~
24 ~~reviewed~~ [are lack of high-quality synthesis of current evidence](#). Thus, this systematic review is
25 conducted to assess the efficacy and safety of acupuncture for PHN in pain-relieving and
26 pain-removing.
27

28 **METHODS AND ANALYSIS**

29 **Criteria for considering studies for this review**

30 **Type of studies**

31
32 Randomized controlled trials (RCTs) will be included without restriction of language or
33 publication type. Moreover, the trials using open label, single blind and double blind design will
34 all be included, while cross-over designs and quasi- RCTs will be excluded.
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53 Studies with the following comparisons will be included:

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~~1-~~ [as measured by](#) [Studies which applied scales such as](#) Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), the Faces Pain Scale-Revised (FPS-R), etc. [that were used to measure the intensity of pain will be included.](#)

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26 **Data synthesis**

27 The Revman 5.1 software will be used to conduct Meta analysis and calculate the RR with 95%CI
28 for the dichotomous data, the WMD or the SMD with 95%CI for continuous data during synthesis.
29 If the same outcome measurement tool and unit is used, the WMD with 95%CI will be calculated,
30 or SMD with 95%CI instead. If the included studies exist heterogeneity, the P value is less than
31 0.1, the RR, the WMD, or the SMD will be calculated by the random effects model. Otherwise, it
32 will be calculated by a fixed effect model.
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35 **Subgroup analysis**

36 Subgroup analysis will be performed based on different controls, interventions, durations of
37 treatment, and outcome measures. Adverse effects will be tabulated and assessed with
38 descriptive techniques.
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40 **Sensitivity analysis**

41 For the sensitivity analysis, the meta-analysis will repeat, substituting decisions alternatively to
42 test the robustness of the primary decisions of the review process ^[27]. The decision nodes are
43 principally the methodological qualities, the sample size and the option of using missing data
44 (available case analysis and full intent-to-treat analysis).
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47 **Discussion DISCUSSION**

48 PHN brings a significant adverse impact on patients' daily activities, quality of life, general health,
49 psychological health, and social and economic well-being. Acupuncture therapy is a suggested
50 intervention in China that may have value to treat PHN, but no high-quality synthesis of the
51 evidence exists. [Thus, a high-quality systematic review is needed and the process of performing
52 this study can be found in figure 1 which will be separated into four parts: identification,
53 selection, data extraction and management, and data analysis.](#)
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7 This study might have kind of limitations that may limit its ability to generate conclusions based
8 on high confidence. Specifically, there may be significant heterogeneity in the forms of
9 acupuncture therapies used and the qualities of methodology. There will also likely be
10 differences in outcomes measured and tools used. Inherent uncertainty exists by pooling this
11 data within constructed domains.
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14 This review has not searched studies in more electronic databases or a grey list, which could limit
15 the broad search of RCTs to generate the findings.
16

17 **Conclusion**

18 ~~This systematic review will accumulate the current evidence on the efficacy and safety of~~
19 ~~acupuncture for PHN. And it will benefit policy makers, patients, and clinicians seeking innovative~~
20 ~~and effective ways to achieve pain relief and removal for PHN.~~
21

22
23 **Authors' contributions:** Wang LI and Zhishun LIU contributed to the conception of the study. The manuscript of
24 the protocol was drafted by Wang LI, and was revised by Weina PENG. The search strategy was developed by all
25 authors and run by Wang LI and Jing ZHOU, who will also independently screen the potential studies, extract data
26 of included studies, assess the risk of bias and finish data synthesis. Zhishun LIU will arbitrate the disagreements
27 and ensure that no errors occur during the study. All authors approved for the publication of the protocol.
28

29
30 **Funding statement:** This research received no specific grant from any funding agency in the public, commercial
31 or not-for-profit sectors.
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34 **Competing interests:** No competing interests exist.
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37 ~~Ethical approval: This research does not need ethical approval because data we used will not be linked to~~
38 ~~individual data and privacy.~~
39

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For peer review only

Appendices

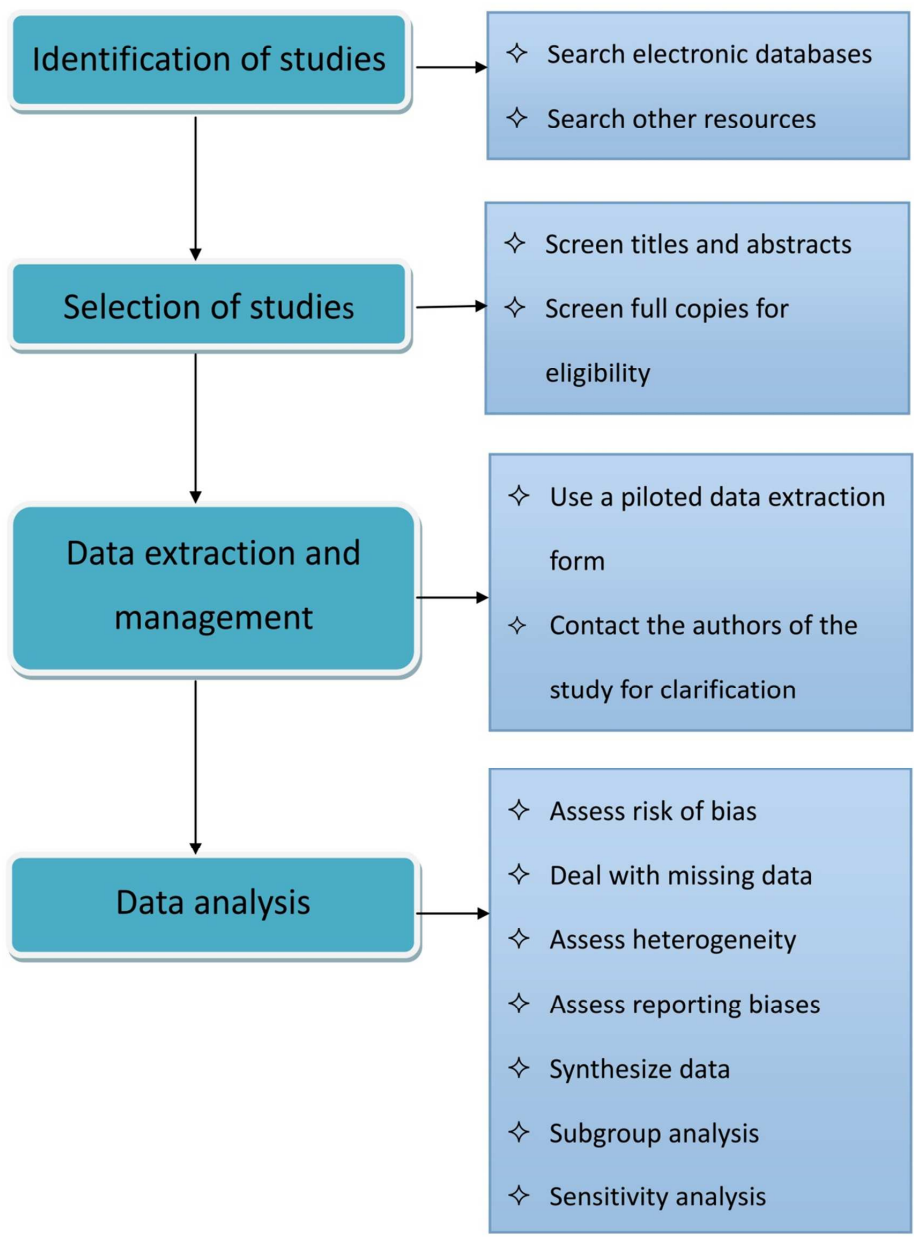
Appendix 1. OVID MEDLINE search strategy

1. randomized controlled trial. pt.
2. controlled clinical trial. pt.
3. randomized. ti, ab.
4. randomly. ti, ab.
5. trial. ti, ab.
6. groups. ti, ab.
7. or/1-6
8. exp acupuncture therapy, or acupuncture
9. acupressure. ti, ab.
10. (acupoint \$ or electroacupuncture or electro-acupuncture). ti, ab.
11. elongated needle \$. ti, ab.
12. (three edged needl \$ or three-edged needl). ti, ab.
13. (fire needling or warming needl). ti, ab.
14. auricular acupuncture. ti, ab.
15. pyonex. ti, ab.
16. moxibustion. ti, ab.
17. (pricking blood or bloodletting or blood-letting). ti, ab..
18. cupping. ti, ab.
19. Or/8-18
20. exp postherpetic neuralgia, or post-herpetic neuralgia
21. PHN. ti, ab.
22. herpes zoster. ti, ab.
23. shingles. ti, ab.
24. (neuralgia or postherpetic) . ti, ab.
25. herpes zoster. ti, ab.
26. Or/20-25
27. 7 and 19 and 26

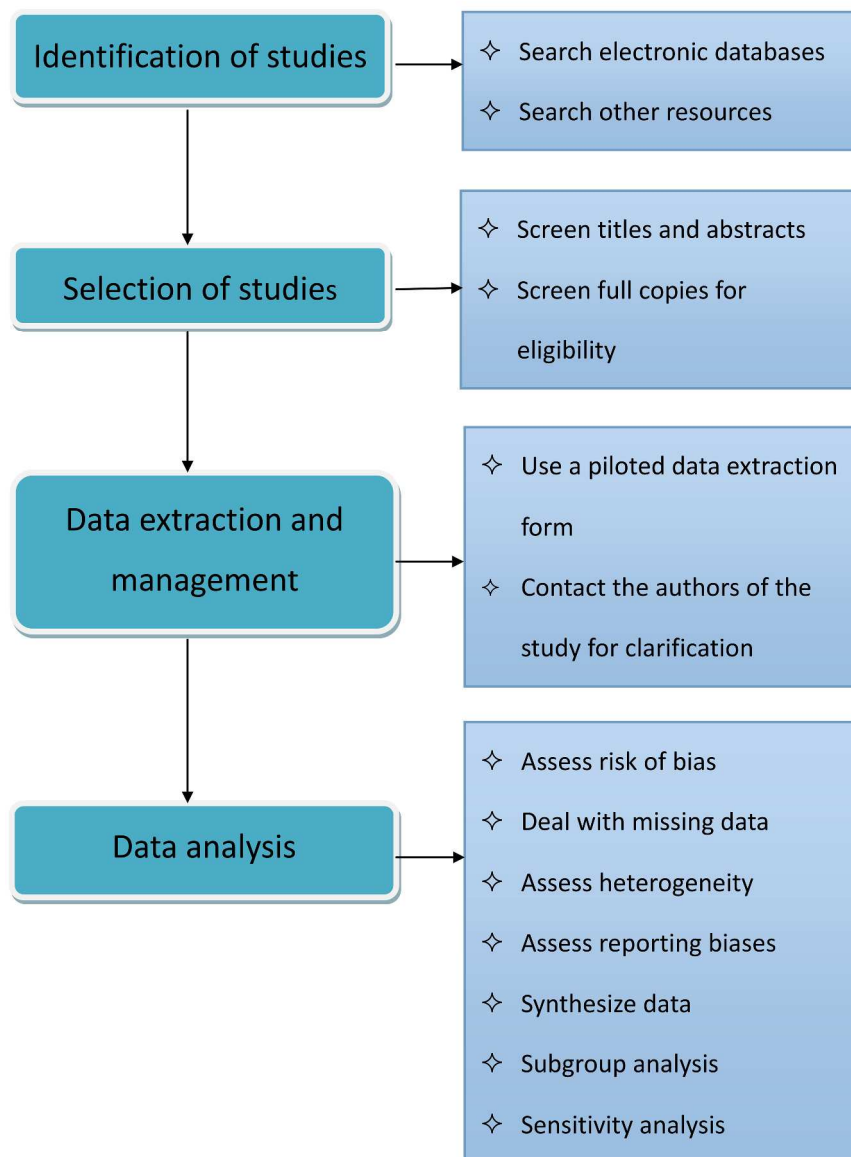
This search strategy will be suitable for other electronic databases.

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Appendix 2 Figure 1. Flow chart of the systematic review



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Flow chart of the systematic review
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Appendix 1. OVID MEDLINE search strategy

1. randomized controlled trial. pt.
2. controlled clinical trial. pt.
3. randomized. ti, ab.
4. randomly. ti, ab.
5. trial. ti, ab.
6. groups. ti, ab.
7. or/1-6
8. exp acupuncture therapy, or acupuncture
9. acupressure. ti, ab.
10. (acupoint \$ or electroacupuncture or electro-acupuncture). ti, ab.
11. elongated needle \$. ti, ab.
12. (three edged needl \$ or three-edged needl). ti, ab.
13. (fire needling or warming needl). ti, ab.
14. auricular acupuncture. ti, ab.
15. pyonex. ti, ab.
16. moxibustion. ti, ab.
17. (pricking blood or bloodletting or blood-letting). ti, ab..
18. cupping. ti, ab.
19. Or/8-18
20. exp postherpetic neuralgia, or post-herpetic neuralgia
21. PHN. ti, ab.
22. herpes zoster. ti, ab.
23. shingles. ti, ab.
24. (neuralgia or postherpetic) . ti, ab.
25. herpes zoster. ti, ab.
26. Or/20-25
27. 7 and 19 and 26

This search strategy will be suitable for other electronic databases.