


BMJ Open Efficacy and safety of acupuncture for recurrent aphthous stomatitis: a systematic review protocol

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ABSTRACT

Introduction Recurrent aphthous stomatitis (RAS) is a distressing symptom. There are many ways to treat RAS, such as pudilan anti-inflammatory oral liquid and doxycycline and laser therapy, but these take a long time to produce positive effects and compliance is low. Previous reviews of acupuncture treatment for RAS has been growing, but a systematic review is not available. To assess the efficacy and safety of acupuncture for the management of RAS.

Methods and analysis The following databases will be searched from their inception to 1 February 2020: PubMed, Embase, Cochrane Library, CINAHL, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure and Wanfang. The randomised controlled trials in English or Chinese associated with acupuncture for patients with RAS will be included. Eligible study conference abstracts and reference lists of manuscripts will also be searched. Two reviewers will select the studies, extract data independently. The Cochrane risk of bias tool will be used to assess the risk of bias for the studies. According to heterogeneity testing, data will be synthesised using a random-effects model. A meta-analysis will be performed using Rev Man V.5.3.5 statistical software for each outcome. Subgroup analysis and sensitivity analysis are planned according to clinical evidence. Mean difference or standardised mean difference for continuous data and risk ratio for dichotomous data will be calculated.

Ethics and dissemination No ethical approval is required. This protocol will not involve individual patient information and endangering participant rights. The results will be reported in a peer-reviewed journal or disseminated in relevant conferences.

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a common oral mucosal disease worldwide problem, with a prevalence of 0.5%–75%.¹ RAS often occurs between the age of 10 and 19, with no sex predilection.² Importantly, growing evidence confirms that deficiencies of iron and vitamins B₉, B₁₂ or D and Zinc which may cause RAS.³ Patients are characterised by symptoms, including circular or oval ulcers with circumscribed margins located on

Strengths and limitations of this study

- This protocol was conducted to evaluate the efficacy and safety of acupuncture on recurrent aphthous stomatitis.
- The systematic review may assist in clinician clinical treatment.
- Two independent reviewers will identify eligible studies.
- Few studies with a high risk of bias might affect the quality of results.
- The various types of acupuncture may increase the risk of heterogeneity.

the buccal and labial mucosa and tongue.^{4 5} These can result in substantial painful symptomatology.⁶ In addition, a study has been reported drinking, eating, talking and other stimulation can cause mucosal wound burning.⁷ RAS will reduce the quality of life of patients, the most common situation is the discomfort when eating, which cause patients lack of nutrition.⁸

The treatment methods are non-specific and based on experimental studies.^{4 9} Glucocorticoids are used to RAS as the first-line treatment, but the use of medium and high potency corticosteroids in the oral cavity because of considerable side effects, such as mucosal atrophy and predisposing.¹⁰ Although many therapeutic interventions are available to recurrent oral ulcer patients; the long-term use can be associated with a number of adverse events. Patient may also suffers fear from incurative treatment exists for RAS.¹¹ The interest in non-pharmacological treatments are needed to alleviate recurrent oral ulcer among patients, including acupuncture, tuina and physical therapy.

Traditional Chinese Medicine treatment can significantly reduce the severity of the disease in patients with ulcer.¹² Acupuncture is a safe medical procedure with minimal side effects. It stimulates acupoints in the meridians

by using sterile needles. Emerging reports suggest that acupuncture may be effective in treating RAS. Wang T study¹³ reported clinical observation of recurrent oral ulcer with acupoint injection and fire needling therapy. Chen's study¹⁴ shows that acupuncture has better effect compared with traditional western medicine group. The clinical practice of acupuncture comprises procedures that entail different needle manipulation techniques insertion of needles into subcutaneous tissue or muscles at acupuncture points. Acupuncture is commonly used as a safe treatment for patients in China.

From the perspective of research design for clinical trials, acupuncture included a variety of methods. These interventions included manual acupuncture, electroacupuncture, auricular acupuncture and body or auricular acupressure. However, the effect of the different types of acupuncture has not been synthesised. Briefly, there is lack of evidence on the contribution of acupuncture in the treatment of RAS patients. Therefore, we designed this study to systematically assess the efficacy and safety of acupuncture for treating RAS.

Patients, intervention, comparison and outcome strategy

Patients: participants had been diagnosed with RAS.

Intervention: acupuncture (manual acupuncture, electroacupuncture, auricular acupuncture) and acupressure (body or auricular acupressure)

Comparison: sham acupuncture, placebo acupuncture, no acupuncture, conventional western medicine.

Outcome: ulcer healing time, recurrent oral ulcer scores, the signs and symptoms of scores, Visual Analogue Scale (VAS) assessment scores, ulcer relapses after treatment, frequency of pain attacks, safety of the acupuncture intervention including adverse events.

METHODS AND ANALYSIS

Study registration

This protocol has followed Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

Inclusion/ exclusion criteria for study selection

Types of studies

All randomised controlled trials (RCTs) of acupuncture for RAS will be included. We will include two-arm or three-arm parallel studies. Animal studies, case reports, quasi-RCTs will be excluded.

Types of participants

We will include trials in which study participants had been diagnosed with RAS. The study population initially included age, gender or previous and current pathologies.

Types of interventions

Studies in which the effects of acupuncture (manual acupuncture, electroacupuncture, auricular acupuncture) and acupressure (body or auricular acupressure) was compared with control group (sham acupuncture, placebo acupuncture, no acupuncture, conventional

western medicine). Moxibustion, point-injection and other types of acupuncture will also be included. Massage and herbal medicine will be excluded. However, studies that evaluated the efficacy of different types of acupuncture will be excluded. There will be no restrictions by patients who have undergone acupuncture treatment frequency. We will include studies with the number of sessions or estimated contact hours and severity of pain and safety of treatments.

Types of outcome measures

Primary outcomes

Ulcer healing time.

Secondary outcomes

1. Recurrent oral ulcer scores.
2. The signs and symptoms of scores.
3. VAS assessment scores.
4. Ulcer relapses after treatment.
5. Frequency of pain attacks.
6. Safety of the acupuncture intervention including adverse events.

Search strategy

The following databases will be searched from their inception to 1 February 2020: PubMed, Embase, Cochrane Library, CINAHL, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure and Wanfang. The RCTs in English or Chinese associated with acupuncture for patients with RAS will be included. Eligible study conference abstracts and reference lists of manuscripts will also be searched. The proposed full search strategy for PubMed is shown in [box 1](#).

Searching other resources

The ongoing or unpublished trials will also be searched on the NIH clinical registry ClinicalTrials.gov, the US National Institutes of Health Ongoing Trails Register, the WHO International Clinical Trials Registry Platform, the Australian New Zealand Clinical Trials Registry and the Chinese clinical registry.

Data collection and analysis

Data extraction and management

Two independent reviewers (FZ and HZ) will identify eligible studies after reading titles and abstracts. DZ and SD will read the full texts to perform further selection. The entire process of selection (reading full text) will be done independently by at least two reviewers, with any disagreements resolved by the reviewer (CW). The process of identifying is screening are clarified for systematic reviews and meta-analyses flow chart ([figure 1](#)). The data extraction (DL and XC) from includes the following items: the first author, year, country, participants, randomised, blind, type of acupuncture, time of treatment, follow-up, outcome measures, results and adverse events.

Box 1 Search strategy in PubMed database
Search items

1. Randomized controlled trial.Mesh.
2. Controlled clinical trial.ti.ab.
3. Randomized.ti.ab.
4. Randomly.ti.ab.
5. Trial. ti.ab.
6. 1 or 2–5.
7. Recurrent aphthous stomatitis.Mesh.
8. Recurrent aphthous stomatitis.ti.ab.
9. Aphthous stomatitis.ti.ab.
10. Aphthous.ti.ab.
11. Stomatitis.ti.ab.
12. 7 or 8–11.
13. Recurrent oral ulcer.Mesh.
14. Recurrent oral ulcer.ti.ab.
15. Oral.ti.ab.
16. Ulcer.ti.ab.
17. 16 or 17–20.
18. Acupuncture.Mesh.
19. Acupuncture therapy.ti.ab.
20. Acupuncture points.ti.ab.
21. Manual acupuncture.ti.ab.
22. Electroacupuncture.ti.ab.
23. Auricular acupuncture.ti.ab.
24. 18 or 21–25.
25. Acupressure.Mesh.
26. Body acupressure.ti.ab.
27. Auricular acupressure.ti.ab.
28. 6 and 12 and 17 and 26.

Assessment of risk of bias

Risk of bias will be carried out by three independent reviewers (FZ, HZ and SD) using the Cochrane Collaboration's tool version 2.0. The modified Cochrane Collaboration tool will be conducted as either: 'unclear', 'low' or 'high' risk for the following criteria: random sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other bias.

Any discrepancies will be resolved by discussion with a four reviewer (CW).

Measures of treatment effect

Dichotomous outcomes (the signs and symptoms of scores, ulcer relapses after treatment, safety of the acupuncture intervention including adverse events) data will be conducted using the risk ratio with 95% CIs. OR and relative risk are commonly used. For continuous outcomes (ulcer healing time, recurrent oral ulcer scores, VAS assessment scores, Frequency of pain attacks), the weighted mean difference or the standard mean difference will be analysed.

Unit of analysis issues

The unit of analysis will be performed based on the study summary statistics.

Dealing with missing data

As mentioned, the missing data or insufficient reporting of details, the corresponding author will be contacted to complement the contents. In case of missing data cannot be obtained; the available data will be analysed. A sensitivity analysis will be adapted to address the missing data.

Assessment of heterogeneity

The heterogeneity for all studies will be conducted by Review Manager (V.5.3.5). χ^2 test and the forest plot will be measured by software. Statistical heterogeneity among studies will be calculated using the I^2 value. The I^2 value is classified into four levels: little or no heterogeneity (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%) and considerable heterogeneity (75%–100%).¹⁵ To explore potential sources of heterogeneity, sensitivity analysis or subgroup analysis will be used to evaluate.

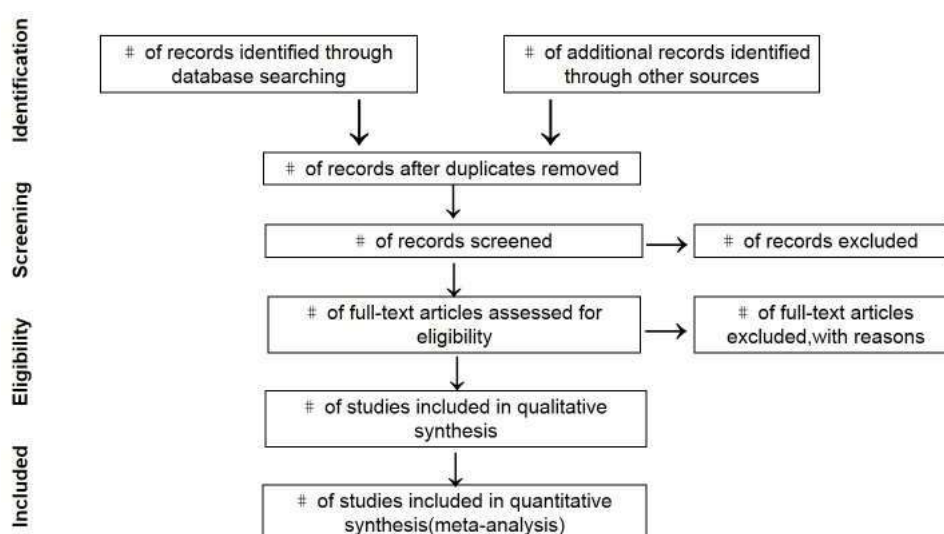


Figure 1 Flow diagram of the trial selection process.

Assessment of reporting biases

As described for the reporting biases, we will conduct funnel plots (more than 10 studies).¹⁵

Data synthesis

The results will be analysed based on Review Manager (V.5.3.5) with random-effects model adopted as inferences are required over the population of possible trials. Each subgroup will be performed for subgroup analysis and sensitivity analysis. If necessary, a narrative, the qualitative summary will be provided.

Subgroup analysis and investigation of heterogeneity

When the data of studies are possible and appropriate, subgroup analysis will be conducted to explore potential sources of heterogeneity. Subgroup analyses will be used to interpret the heterogeneity according to types of acupuncture (manual acupuncture, electroacupuncture, auricular acupuncture) and acupressure (body or auricular acupressure), type of control (sham acupuncture, placebo acupuncture, no acupuncture, conventional western medicine).

Sensitivity analysis

Sensitivity analysis will be performed to assess the robustness of the results and used to determine whether the conclusions are robust to the decisions made according to methodological quality, sample size and analysis-related issues. Furthermore, a sensitivity analysis will be presented according to methodological quality, sample size and statistical model by the Cochrane Handbook. The χ^2 test and I^2 value will be performed to quantify statistical heterogeneity.

Summary of evidence

The reviewers (SD and DZ) will use the Grading of Recommendations Assessment, Development and Evaluation approach,¹⁶ including high, moderate, low and very low quality. The assessment includes the risk of bias, heterogeneity, indirectness, imprecision and publication bias.

Patient and public involvement

No patient involved.

DISCUSSION

RAS is common symptoms for patients. However, the aetiology of RAS remains unknown. A previous study¹⁷ found that RAS is caused by immunological. Bacterial agents can interfere with the development of RAS.¹⁸ In recent decades, the bee product propolis and lactic acid 5% mouth wash have attracted interest from clinicians for RAS treatment.¹⁹ Acupuncture is increasingly used by patients with RAS to help treat symptoms. Recent advances from published clinical trials have added evidence for the management of RAS in patients.²⁰ Acupuncture has been shown to regulate the flow of 'Qi', by the stimulation of certain points on the body.²¹ Acupuncture, a safe

technique, could significantly reduce symptoms induced by RAS and enhance the quality of life in patients. In addition, the acupressure treatment is easy to learn and can be self-administered in patients.

This systematic review will evaluate published RCTs evidence for the efficacy and safety of acupuncture for RAS. Also, it may assist clinician clinical treatment. Potential limitation of this study may affect results. Restricting the electronic search to the English and Chinese languages may limit the search for potential studies. The various type of acupuncture may increase the risk of heterogeneity.

Contributors FZ and HZ will identify eligible studies after reading titles and abstracts. DZ and SD will read the full texts to perform further selection. Several studies from different opinions will be determined by the CW. Data will be extracted from the original reports by DL and XC. The assessment of the risk of bias will be carried out by FZ, HZ and SD. Any discrepancies will be resolved by discussion with a third CW. SD and DZ will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. FZ conceived the review protocol and drafted the manuscript. CW will monitor each procedure of the review. All authors have read and approved the publication of the protocol.

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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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