

BMJ Open Acupuncture for refractory gastro-oesophageal reflux disease: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Refractory gastro-oesophageal reflux disease (rGORD) is a common disease, affecting patients' quality of life. Since conventional medicines have limitations, like low effective rates and adverse events, acupuncture may be a promising therapy for rGORD. While no related systematic review has been published, the present study is designed to evaluate the efficacy and safety of acupuncture for rGORD.

Methods and analysis PubMed, the Cochrane Central Register of Controlled Trials and Chinese electronic databases, including China National Knowledge Infrastructure, Wan Fang database, VIP, SinoMed and the Chinese Clinical Trial Registry, will be searched from establishment of the database to 31 August 2019. There will be no limitations on language, and all articles will be screened and collected by two reviewers independently. RevMan V.5.3.5 software will be used for meta-analysis, and the conduction of study will refer to the Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines. The efficacy and safety of acupuncture for rGORD will be evaluated based on outcomes, including global symptom improvement, oesophageal sphincter function test measured by high-resolution manometry, quality of life, recurrence rate and adverse events.

Ethics and dissemination There is no necessity for this study to acquire an ethical approval, and this review will be disseminated in a peer-reviewed journal or conference presentation.

Trial registration number CRD42018111912.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a chronic, persistent and common disease. Data from 28 studies of GORD prevalence (defined by either typical symptoms at least once weekly or the Montreal definition¹) indicated that the range of prevalence estimates was 18.1%–27.8% in North America, 8.8%–25.9% in Europe, 2.5%–7.8% in East Asia, 8.7%–33.1% in the Middle East, 11.6% in Australia and 23.0% in South America.² Nowadays, acid suppressive therapy, especially proton pump inhibitor (PPI), is still the first-line approach for GORD.³ However, up to 30% of patients with GORD will continue

Strength and limitations of this study

- This study will provide the first systematic review and meta-analysis for evaluating the efficacy and safety of acupuncture for refractory gastro-oesophageal reflux disease (rGORD).
- Since most randomised controlled trials on acupuncture for rGORD have small sample size, the present study will provide more reliable evidence for clinical management.
- The reliability of the results will largely depend on the methodological quality of primary studies included and the heterogeneity among them.

to experience reflux symptoms despite adequately dosed PPI therapy.^{4,5} GORDs in these patients are usually termed as refractory GORD (rGORD) which is defined as reflux symptoms that fail to respond partially or completely to a standard dose of PPI after 8 weeks' therapy.^{6,7}

Refractory GORD is increasingly challenging gastroenterologists. Patients' quality of life (QOL) can be significantly affected, including sleep and work.⁸ Currently, while increasing the dose of the PPI to twice a day is the standard clinical approach for patients with rGORD, it has various limitations.⁹ A large proportion of patients with rGORD still cannot get symptomatic relief with adequate PPI therapy.¹⁰ Aimed at other mechanisms underlying rGORD, new drugs have been developed in recent years, but most have failed due to lack of efficacy and serious adverse events.^{11–13} Surgery is another option for patients with rGORD symptoms failing medical therapy, but its application is limited by unfavourable outcomes and surgical complications, such as postoperative dysphagia and gas bloat syndrome.³

Complementary medicine, especially acupuncture, may bring new hope for patients with rGORD, just as it does in other diseases.^{14–16} Acupuncture, as an important part of traditional Chinese medicine (TCM),

has been widely used to treat diseases for thousands of years. Guided by the theory of TCM, sterile solid filiform needles are used to penetrate the patient's body based on certain acupuncture points. Certain operation methods, like twirling, lifting and thrusting needles, may be used to achieve effects through the conduction of meridians and acupoints. Due to the advantages, including wide indication, reliable effect, convenient operation, economical and safety, acupuncture has been accepted and applied around the world.¹⁷ It has been used for various gastrointestinal disorders,^{14 18} and a significant effect on GORD and rGORD has also been demonstrated.^{19–21} A meta-analysis including 12 studies has shown that acupuncture is effective in improving global symptoms and QOL, reducing recurrence rate and without adverse events.²⁰ The mechanisms underlying acupuncture's efficacy is still unclear, but may be related to the following aspects: persistent pathological oesophageal acid exposure, weakly acidic reflux episodes and reflux hypersensitivity have been thought to be responsible for rGORD.²² Studies showed that acupuncture therapy may decrease the duration of oesophageal acid exposure and increase lower oesophageal sphincter pressure which reduces pathological oesophageal acid exposure and weakly acidic reflux episodes.^{23–25} Furthermore, since efficacy of acupuncture on visceral hypersensitivity in irritable bowel syndrome has been demonstrated, there may also be a modulatory effect on oesophageal sensory thresholds.^{26 27}

However, no consensus on the efficacy of acupuncture for rGORD has been reached. Since most trials on acupuncture for rGORD have small sample size, we will conduct the first systematic review and meta-analysis, to our knowledge, to provide more reliable evidence for evaluating the efficacy and safety of acupuncture for rGORD.

METHODS

Patients and public involvement

Patients and public will not be involved in this study.

The protocol follows the Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines.^{28 29} We will describe the changes in our full review if needed. The study will be started on 1 September 2019.

Eligible criteria for study selection

Types of studies

Randomised controlled trials assessing the efficacy of manual acupuncture or electroacupuncture for patients with rGORD will be included, regardless of whether the blind method is used or not. Language and publication time are unlimited.

Types of participants

Patients of any age or sex diagnosed with rGORD will be included. The diagnosis of rGORD is based on Asia-Pacific consensus on the management of GORD (2016).⁶

Types of interventions

Interventions will include manual acupuncture or electroacupuncture, used alone or in combination with western medicines, which should be the same as those used in the control groups. No limitations will be placed on treatment duration. Western medicines, such as PPIs and histamine-2 receptor antagonists, with or without sham acupuncture can be provided for control groups.

Types of outcome measures

Primary outcomes

Global symptom improvement will be evaluated as the primary outcome. The main evaluation indicators include main characteristics of heartburn, regurgitation and chest pain: duration, frequency and intensity.

Secondary outcomes

The secondary outcomes mainly include the following aspects: oesophageal sphincter function test measured by high-resolution manometry, QOL, recurrence rate and adverse events.

Searching methods for the identification of studies

A literature search from inception in PubMed, the Cochrane Central Register of Controlled Trials and the Chinese electronic databases, including China National Knowledge Infrastructure, Wan Fang database, VIP, SinoMed and the Chinese clinical trial registry, will be independently carried out by two investigators (LZ and DL), using terms 'acupuncture', 'electroacupuncture', 'refractory', 'persistent', 'troublesome', 'proton pump inhibitor-resistant', 'GERD', 'GORD', "NERD", 'erosive esophagitis', 'gastroesophageal reflux disease', 'non-erosive reflux disease', 'gastro oesophageal reflux disease', 'nonerosive esophagitis', 'endoscopically negative reflux disease'. The maximum number of articles will be sought using terms in all possible combinations. There will be no limitations on language, and the last search update will be undertaken on 31 August 2019.

Data collection

Selection of studies

Included articles will be independently reviewed by two authors (DL and LZ), based on title/abstract first and full-text second. During the process of full-text selection, disagreements will be resolved by discussion, and if an agreement cannot be reached, a third author (DLiu) will make a decision. If a consensus still cannot be reached, the dispute will be settled by contacting the original author for original data. The process of study selection is shown in [figure 1](#).

Data extraction and management

A predefined data template will be prepared, including following information: study characteristics, participants, interventions, outcome measures, adverse events and follow-up date. The template will be presented to two reviewers (DL and LZ), who will independently extract and code the data based on the template, respectively.

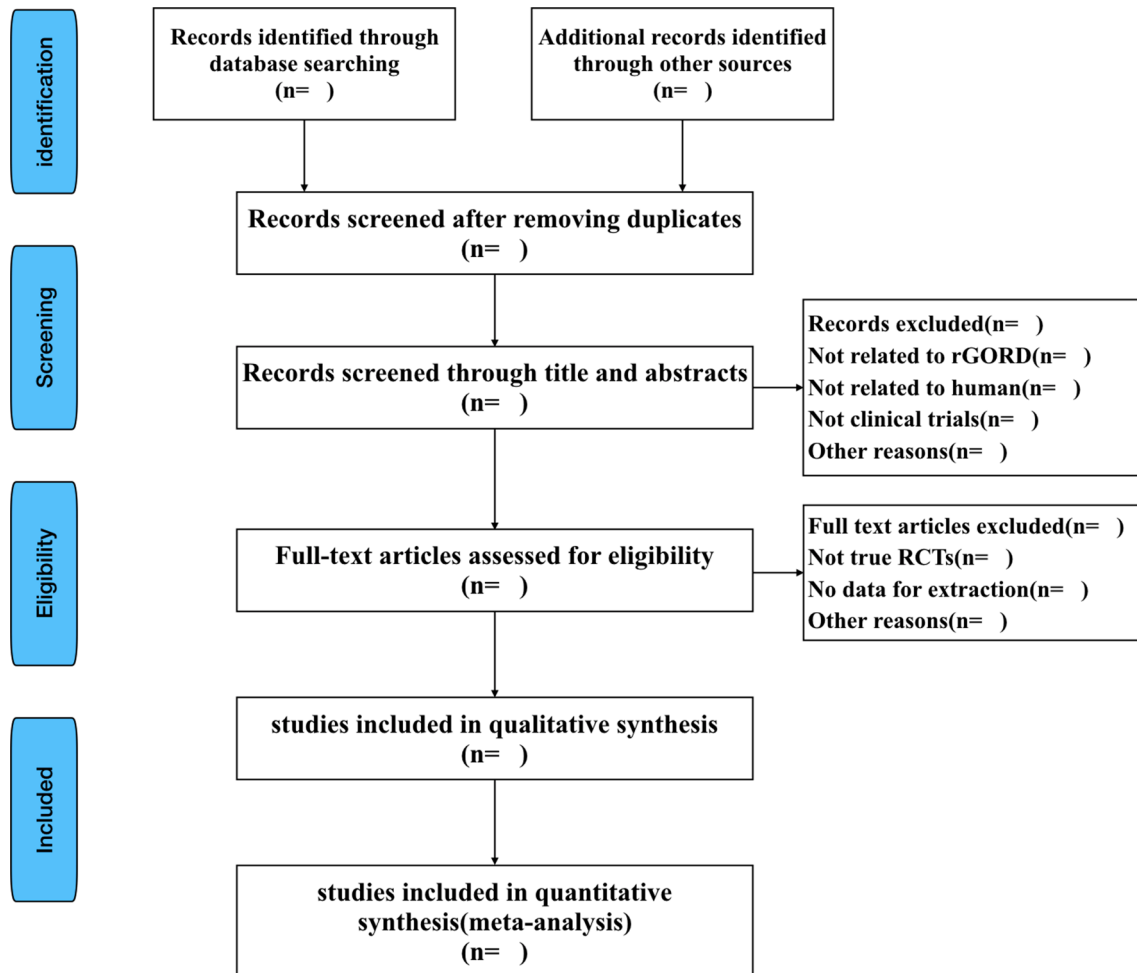


Figure 1 Flow diagram of the study selection process. RCT, randomised controlled trial; rGORD, refractory gastro-oesophageal reflux disease.

Finally, data obtained by the two reviewers will be checked, and if there is a difference, it will be discussed by reviewers. On condition that some data are missing, we will contact the original author or transform existing data.

Assessment of risk of bias

Using the Cochrane risk of bias tool, the methodological qualities of the included trials will be evaluated by two researchers (DL and LZ) which will be based on six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, incomplete outcome data and other bias. The risk of bias for the individual domains will be classified as low, unclear (insufficient information provided) or high, and the results from the six domains will be combined into an overall score which will be classified as low if all six individual domains are considered to have a low risk of bias and high if one or more of the domains is considered to have an unclear or a high risk of bias. Disagreements will be resolved through discussion and consensus with a third researcher (DLiu).

DATA ANALYSIS

Data synthesis

RevMan V.5.3.5 (Cochrane, London, UK) will be used to analyse the data. Trials examining same intervention and outcomes in similar populations will be combined to estimate pooled intervention effect using the meta-analysis. Dichotomous data will be expressed as relative risk and continuous variables as mean difference (MD) with 95% CI. Standardised MD and 95% CI will be used for continuous variable when the units are different. We will pool the continuous data using the inverse variance method and dichotomous data using the Mantel-Haenszel method. It is considered statistically significant when $p < 0.01$.

Assessment of heterogeneity

Both the χ^2 test and I^2 statistics will be used for the assessment of heterogeneity, and a fixed effect model will be used if there is no obvious heterogeneity ($I^2 < 50\%$ and $p > 0.1$), with a random effects model being used if significant heterogeneity is found to exist ($50\% < I^2 < 80\%$ or $p < 0.01$).

Subgroup analysis and sensitivity analysis

Subgroup analysis and sensitivity analysis will also be performed to explore the possible causes of heterogeneity.

If the necessary data are available, subgroup analyses will be carried out for the different acupuncture interventions (eg, acupuncture/electroacupuncture vs acupuncture/electroacupuncture combined with PPIs), different types of control group (western medicines with or without sham acupuncture), length of treatment, and duration, frequency and severity of symptoms at baseline. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

Assessment of publication bias

If more than 10 articles are included, publication bias will be analysed by visual inspection of funnel plots. A symmetrical distribution of funnel plot data indicates that there is no publication bias.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation guidelines will be performed to assess the strength of the body of evidence for primary outcomes which will be graded into very low, low, moderate or high level.

ETHICS AND DISSEMINATION

There is no necessity for this study to acquire an ethical approval, since no private information of participants will be involved. Results of the present study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated on PROSPERO.

Contributors DLiu and DL designed this study, and DLiu is the guarantor for the article. DL drafted the protocol, which was revised by DLiu and LZ. DL and LZ will search, select, and identify studies included, and extract data independently, while DL will be the third reviewer for study selection and data extraction. LZ will serve as an adviser for methodology. All authors have approved the publication of this protocol.

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Competing interests None declared.

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