Acupuncture for Crohn’s disease: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Crohn’s disease (CD) is a chronic inflammatory bowel disease that seriously affects the quality of life. While conventional medicines are of limitations, acupuncture has been shown to be a promising therapy. While no systematic review related has been published, the present study aimed to evaluate the efficacy and safety of acupuncture for CD.

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 the establishment of the database until 31 December 2022. Randomised controlled trials evaluating the efficacy and safety of acupuncture/electroacupuncture on patients with CD, controlled by conventional therapies, were included. Outcomes include induction of clinical remission and response, maintenance of remission, and the incidence of adverse events. All articles will be screened and extracted by two reviewers independently. The risk of bias will be evaluated using the revised Cochrane Risk of Bias 2 tool. A fixed effect model or a random effects model will be used based on the assessment of heterogeneity. A subgroup analysis and sensitivity analysis will be carried out if necessary. Publication bias will be analysed, and the strength of the body of evidence for primary outcomes will be graded.

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

Trial registration number CRD42022356967.

INTRODUCTION

Crohn’s disease (CD) is a chronic inflammatory bowel disease characterised by abdominal pain, diarrhoea, fatigue and weight loss. It seriously affects the quality of life and results in long-lasting physical and psychological effects on patients.1 In the past decades, the incidence and prevalence of CD has gradually increased worldwide, especially in newly industrialised countries such as China.2 While the conventional therapy, including 5-aminosalicylic acid preparations, glucocorticoids and immunomodulators, are all of various limitations, biological therapy has brought dawn to the treatment of CD in recent years.3 4 However, despite the undisputed efficacy of biological agents, a considerable proportion of patients still fail to induce and maintain remission.5

Acupuncture, as an important part of traditional Chinese medicine (TCM), has been widely used to treat gastrointestinal diseases for thousands of years. Guided by the theory of TCM, special needles are inserted into specific acupuncture channels and points on the body to correct the disruptions in harmony.6 While the long-term clinical practice has shown the efficacy of acupuncture on relieving abdominal symptoms, such as abdominal pain and diarrhoea, studies also demonstrated that acupuncture might be effective in treating inflammatory bowel diseases.7–13 Bao et al’s randomised controlled trial (RCT) showed that acupuncture was effective in inducing and maintaining remission in patients with active CD during 48 weeks.7 Both Guo et al and Joos et al found a significant decrease of CD activity index (CDAI) score in patients with CD and treated by acupuncture combined with moxibustion.8 9 Bao et al’s another study also confirmed the effect of electro-acupuncture on CD.10

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first systematic review to evaluate the efficacy and safety of acupuncture for Crohn’s disease.
⇒ We will conduct a comprehensive search in both the Chinese and English databases.
⇒ The collection and analysis of data will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.
⇒ Detailed subgroup analysis based on types of interventions and the severity of disease will help us to assess the efficacy in depth.
⇒ The quality of original researches may cause considerable heterogeneity and affect the reliability of our results.
Furthermore, a meta-analysis including 13 studies has shown that both acupuncture alone and acupuncture combined with conventional medicine may be effective in treating ulcerative colitis, which is collectively known as inflammatory bowel disease with CD. However, no consensus on the efficacy of acupuncture for CD has been reached.

Therefore, we would like to perform a meta-analysis of trials evaluating the efficacy and safety of acupuncture for CD, which to our knowledge, will be the first systematic review in this area.

METHODS AND ANALYSIS

Study registration
This systematic review protocol has been registered on PROSPERO and is available from: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=356967. The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement guidelines. We will describe the changes in our full review if needed.

Patient and public involvement
No patients or the public were involved.

Search strategy
A literature search 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 (QH and DL), using terms “acupuncture”, “electroacupuncture”, “electro-acupuncture”, “Crohn’s disease”, “inflammatory bowel disease”, “CD”, “IBD”. 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 December 2022.

Eligible criteria

Study design
Only RCTs assessing the efficacy and safety of acupuncture for CD will be included. Language and publication time are unlimited.

Participants
Patients of any age or sex diagnosed with CD will be included. The diagnosis of CD is defined by clear diagnostic criteria or references. In particular, patients with unclassified inflammatory bowel disease will not be included.

Interventions/comparators
Interventions will include manual acupuncture or electroacupuncture, used alone or combined with Western medicines, which should be the same as those used in the control groups.

Outcomes
Induction of clinical remission will be evaluated as the primary outcome, defined as CDAI <150 within 12 weeks and within 52 weeks. The secondary outcomes mainly include the following aspects: induction of clinical response defined as a decrease in CDAI score by ≥70 from baseline, maintenance of remission, serum C reactive protein level, endoscopic scores including the CD endoscopic index of severity or the simple endoscopic score for CD, and the incidence of adverse events.

Data collection
Study selection
Two authors (QH and DL) will review all included articles independently, based on title/abstract first and full-text second. During the process of full-text screening, disagreements will be resolved by discussion, and if necessary, the original author will be contacted for original data. A third author (PZ) will make a decision if an agreement cannot be made. The process of study selection is shown in figure 1.

Data extraction
A predefined data template will be provided, including the following information: study information, characteristics of participants, interventions, controls, outcomes, adverse events and follow-up date. Two reviewers (QH and DL) will independently extract and code the data based on the template. Data obtained by the two reviewers will be checked. On condition that some data are missing, we will contact the original author or transform existing data.

Figure 1 Flow diagram of the study selection process.

Only western medicines, such as glucocorticoids, immunomodulators and biological agents, can be provided for control groups, with clear description of dosage and treatment duration.
Risk of bias
Using the revised Cochrane Risk of Bias 2 tool, the methodological qualities of the included trials will be evaluated by two researchers (QH and DL), which will be based on six domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result and bias due to competing risks. The risk of bias for the individual domains will be classified as low, probably low, probably high, high or no information. 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 at least one domain is considered to have a high risk of bias or multiple domains are judged to have some concerns. Disagreements will be resolved through discussion and by consulting a third researcher (PZ).

Data analysis

Data synthesis
RevMan V.5.4.1 (Cochrane, London, UK) will be used to analyse the data. Dichotomous data will be expressed as relative risk and continuous variables as mean difference with 95% CI. Standardised mean difference and 95% CI will be used for continuous variable when the units are different. It is considered statistically significant when p<0.01.

Assessment of heterogeneity
Both the $\chi^2$ 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% or $p>0.1$), 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
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 conventional therapy), different types of western medicines in the control group (eg, glucocorticoids, immunomodulators and biological agents), disease severity (eg, mild-to-moderately severe disease vs moderate-to-severe disease) and treatment duration, etc. To address potential heterogeneity due to pooling studies with different risk of bias, a sensitivity analysis was performed by excluding studies with high risk of bias.

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.

DISCUSSION
CD is a chronic progressive and destructive disease, strongly affecting patients in a multitude of ways. Conventional treatments, including biological therapy, have kinds of limitations. As many studies have shown, acupuncture may be helpful in inducing and maintaining remission in CD.\textsuperscript{16} Considering the small sample size of previous studies, our systematic review will first provide higher level evidence and attract more attention to acupuncture for CD.

The mechanisms underlying acupuncture’s efficacy is still unclear. Pathogenesis of CD mainly involves impaired intestinal barrier function, dysregulation of innate and adaptive immune responses, and altered gut microbiota.\textsuperscript{17} Liu et al’s study provided a neuroanatomical basis for the anti-inflammatory effects of electroacupuncture.\textsuperscript{18} Other studies also suggested that acupuncture therapy may regulate numbers and function of various immune cells and cytokines,\textsuperscript{19-21} which was also confirmed in researches on acupuncture for CD. Some studies showed that the biological mechanisms might be related to the balance of Th1, Th17 and Treg cells.\textsuperscript{7 22} Another study showed that acupuncture combined with moxibustion may repair intestinal epithelial barrier lesions and increase tight junction protein expression.\textsuperscript{25} Gut microbiota may also be associated with the mechanisms of acupuncture for CD. It was found that the relative abundance of Faecalibacterium prausnitzii and Roseburia faecis were increased after the treatment of acupuncture.\textsuperscript{7 24}

Our study is certainly not without limitations. The quality of original studies will inevitably affect our results. Different types and courses of acupuncture, and severity of CD may also cause high heterogeneity. Thus, a subgroup analysis will be performed if necessary data are available.

In conclusion, we plan to evaluate the efficacy and safety of acupuncture for CD in the form of a systematic review and meta-analysis for the first time. Our results will provide high-level evidence for the application of acupuncture in the management of CD.

Ethics and dissemination
There is no necessity for this study to acquire 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.

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

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Competing interests None declared.
Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

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REFERENCES