







BMJ Open Effectiveness and safety of acupuncture therapy for inflammatory bowel disease: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction Previous reviews have suggested that the effectiveness of acupuncture for inflammatory bowel disease (IBD) has not well been demonstrated due to the limited randomised controlled trials (RCTs). In recent years, the growing research on acupuncture for IBD make it possible to conduct a further systematic review and synthesise more sufficient clinical data to evaluate the effectiveness and safety of acupuncture for IBD.

Methods and analysis Nine electronic databases without language restriction will be retrieved from inception to March 2021, including the Cochrane Library, MEDLINE, EMBASE, Ovid, the Allied and Complementary Medicine Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, the Chongqing Chinese Science and Technology Periodical Database and Wanfang Database. The RCTs on acupuncture for IBD will be included. The data screening, data extraction and the assessment of risk bias will be performed respectively by two reviewers. The quality of evidence will be evaluated by using the Grading of recommendation Assessment, Development and Evaluation application. The meta-analysis will be performed if heterogeneity analysis conducted on the RevMan software (V.5.3) is insignificant. The primary outcome was symptoms alleviation after acupuncture treatment or even in the follow-up.

Ethics and dissemination Ethical approval will not be needed because data of this review are not involved in patient's information and privacy. The results will be published and diffused in a peer-reviewed journal or relative conferences.

Trial registration number CRD42020157903.

BACKGROUND

The inflammatory bowel disease (IBD) is a chronic intestinal disease characterised by the abdominal pain, diarrhoea and rectal bleeding.¹ It is mainly divided into the Crohn's disease (CD) and ulcerative colitis (UC).² In western countries, the prevalence of IBD is 0.3%–0.6%.^{3–5} And the incidence of IBD in Asia is also gradually growing.^{6 7} In addition, patients with IBD are often accompanied by

Strengths and limitations of this study

- The synthesis of updated data helps provide more evidence of the effectiveness of acupuncture for patients with inflammatory bowel disease (IBD), clinicians and policy-makers.
- The study selection, data extraction and assessment of the risk of bias will be conducted by two or more reviewers independently.
- Different pathogenesis between the IBD subtypes (Crohn's disease and ulcerative colitis) would be a source of heterogeneity, which will be further explored in the subgroup analysis.

emotional disorders and malnutrition, which may result in high medical cost with financial burden and reduced work productivity.^{8–10}

The management of IBD includes drug management (5-aminosalicylic acid, prednisolone, corticosteroids, etc), surgical treatment, nutritional support, antibiotic therapy and lifestyle correction.^{11–13} However, drug management is found causing side effects such as renal toxicity, haemorrhagic risk and headache, etc.^{14–16} Moreover, emergency surgeries for the patients with UC with low preoperative albumin level may result in poor survival.^{17 18} Therefore, an increasing number of complementary and alternative therapies are sought and recommended.^{19 20}

Acupuncture has been used to treat gastrointestinal discomfort in ancient China for thousands of years. Nowadays, it is gradually accepted as a complementary and alternative method for IBD treatment in western countries. A great number of clinical studies have demonstrated the effectiveness of acupuncture for IBD. For instance, Bao *et al* demonstrated that acupuncture might decrease CD patients' abdominal pain, abdominal mass and diarrhoea.^{21 22} Chen and Li and Wen

et al have also found the similar improvement on these symptoms of patients with UC.^{23 24} In addition, it has been reported that acupuncture not only improves IBD patients' quality of life, but also prevents their fatigue.^{25 26}

However, a previous review has suggested that due to the limited high-quality randomised controlled trials (RCTs), the effectiveness of acupuncture therapy for IBD is difficult to be demonstrated.²⁷ With an increasing number of RCTs on the acupuncture for IBD published and registered in recent years, it's necessary to update the systemic review and synthesise more recent data, so as to seek more consistent findings of the effectiveness of acupuncture. Therefore, a systematic review and meta-analysis will be conducted on the current RCTs to prove the clinical effectiveness and safety of acupuncture therapy.

METHODS

Criteria for included studies in this review

Type of studies

RCTs on acupuncture for IBD reported in Chinese or English will be included in this review. Crossover trials, semirandom RCTs and uncontrolled clinical trials will be excluded.

Type of participants

Although the two main subtypes (CD and UC) may have different pathogenesis, they show many common symptoms. To fully prove the effectiveness of complementary and alternative therapies in improving IBD patients' clinical symptoms, trials on patients with IBD, UC or CD of both females and males at any age will be included.

There is no restriction on the diagnostic procedures or settings used in the studies. Studies that focus on patients with other disorders, such as irritable bowel syndrome, acute gastroenteritis, bacillary dysentery, etc will be excluded.

Type of interventions

Body acupuncture (manual/electro), auricular acupuncture, scalp acupuncture and acupoint catgut embedding that describing needle insertion on acupoints, pain points or trigger points will be included. Acupuncture combined with other positive treatment will also be considered. However, other forms of irritating acupoints without needle insertion, such as moxibustion, massage or transcutaneous electrical nerve stimulation will be excluded.

Type of comparator (s)/ control

The included comparators or control groups will be considered as follows:

1. Acupuncture versus sham control.
2. Acupuncture versus routine care.
3. Acupuncture versus conventional drugs.
4. Acupuncture in addition to positive treatment versus positive treatment alone.

The comparators or control groups in studies that comparing clinical efficacy between different acupoints, different methods for stimulating acupoints or comparing acupuncture with other complementary and alternative therapies will be excluded.

Types of outcome measures

Primary outcome

Clinical alleviation after treatment or in the follow-up (s) measured by the CD Activity Index and the Colitis Activity Index.

Secondary outcomes

1. Patients' quality of life, measured by the IBD Questionnaire (IBDQ) or any other validated scales.
2. Patients' emotional status such as anxiety and depression, measured by the Beck Depression Index (BDI), Beck Anxiety Index and any other scales with reliability and validity.
3. Fatigue that patients may feel, measured by the Functional Assessment of Chronic Illness Therapy's fatigue subscale (FACIT-FS) or any other scales with reliability and validity.
4. Adverse events caused by acupuncture such as infection, haematoma, syncope, etc.

Besides, objective indicators such as the serum concentrations of α 1- acid glycoprotein and C reactive protein serum concentrations will also be estimated for more comprehensive evaluation.

Search methods for identifying the included studies

Electronic search

The following databases will be searched from inception to March 2021: the Cochrane Library, MEDLINE, EMBASE, Ovid, the Allied and Complementary Medicine Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, the Chongqing Chinese Science and Technology Periodical Database and Wanfang Database.

The RCTs that evaluate the effectiveness of acupuncture therapy for IBD by setting comparators or controls mentioned above will be included. No restrictions on the language of included studies. The following Medical Search Headings will be searched: (1) IBD, bowel disease inflammatory, colitis ulcerative, CD; (2) acupuncture, acupuncture therapy, electroacupuncture, electroacupuncture therapy, manual acupuncture, auricular acupuncture, scalp acupuncture, abdominal acupuncture, acupoint, acupoint catgut embedding; (3) RCT, randomised controlled, clinical trial. The search terms for MEDLINE are displayed in [table 1](#). In addition, the same searching strategy in Chinese will also be searched in Chinese databases.

Searching other resources

Ongoing trials with unpublished data will be retrieved in clinical trial registries, such as the National Institute of Health (NIH) clinical registry ClinicalTrials.gov (<https://www.clinicaltrials.gov/>), the International Clinical Trials

Table 1 Search strategy used in MEDLINE database

No	Search items
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials [MeSH]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	humans [MeSH]
#10	#8 and #9
#11	inflammatory bowel disease [MeSH]
#12	crohn's disease [MeSH]
#13	colitis, ulcerative [MeSH]
#14	(bowel diseases, inflammatory or crohn's enteritis or regional enteritis or enteritis, Granulomatous or Ileocolitis or colitis, granulomatous or lleitis, terminal or lleitis, regional or Idiopathic proctocolitis or colitis gravis): ti,ab
#15	#11 or #12 or #13 or #14
#16	acupuncture therapy (MeSH)
#17	(acupuncture or body acupuncture or manual acupuncture or electroacupuncture or electro-acupuncture or auricular acupuncture or scalp acupuncture or abdominal acupuncture or acupoint catgut embedding or warm needling): ti,ab
#18	#16 or #17
#19	#10 and #15 and #18

Registry Platform (<http://www.who.int/ictrp/en/>), the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>) and the Chinese clinical registry (<http://www.chictr.org/en/>). The references of all published reviews containing relevant systematic reviews and meta-analyses will be additionally searched with various retrieval methods. The incomplete information for data synthesis will be further obtained by contacting corresponding authors.

Data collection and analysis

Selection of studies

The retrieved studies will be imported in Endnote X9. First, the title and abstract of selected articles will be screened and filtered respectively to assess the eligibility by two reviewers (X-DD and X-YY) according to the inclusion criteria. Second, the full text of qualified studies will be read. The potentially missing trials from the reference list will also be identified by the same two reviewers. Then the final selected studies will be cross-verified by the other two reviewers (X-GX and JZ). Any disagreement will be discussed between the two reviewers and further controversy will be arbitrated by a third reviewer (Z-JL). Each eligible trial will be allocated with an ID, such as zhou

2017. However, each excluded study will be noted with explanation of their excluded reasons in a table. The flow chart of the selection process is shown in [figure 1](#).

Data extraction and management

The information of eligible study will be double-checked by two reviewers (Y-ZQ and L-YH) again. The details of information will be extracted according to the principle of Participant, Intervention, Comparison, Outcome, Setting (PICOS) as following acquisition forms: studies' basic information (title, first author, corresponding author, authors' country, sponsor, journal and time for publication), participants (sample size, gender and age), details of intervention (kinds of intervention, acupoint selection, frequency of treatment) and control (sham control, usual care and management for alleviating symptoms of IBD), outcomes (outcome measurements, adverse events and the follow-up). Standards for Reporting Interventions in Clinical Trials of Acupuncture will be used to check the data extraction of acupuncture techniques.²⁸ And incomplete data will be acquired by contacting the corresponding authors. If there is any disagreement during data extraction, it will be evaluated by the third reviewer (S-RC), and the data will be inputted to the RevMan software (V.5.3) by Y-FZ and NS.

Assessment for risk of bias

The Cochrane Collaboration risk of bias tool will be used for included studies by two reviewers (Y-FZ and NS), respectively.^{29–31} The assessment of risk of bias includes six main domains (random sequence generation, allocation concealment, the blinding of participants, staff and outcome evaluation, incomplete outcome data, selective outcome reporting and other potential bias). Each item will be graded into high risk, low risk or unclear risk. If the trial is evaluated with low risk of bias shows severe heterogeneity on key domains, the trial will be double-checked to redefine its risk of bias. If there is unclear information during the rating of risk of bias, the unclear or even missing data will be tried to acquire by contacting the corresponding author. Any questions or disagreement existing in the final results will be solved by an arbiter (R-RS).

Measures for treatment effect

The inputted data will be synthesised and statistically analysed by using the RevMan V.5.3. The relative risk with 95% CIs will be employed for analysing the dichotomous data (eg, infection or non-infection of adverse events). And the 95% CIs with weighted mean difference (WMD) or a standard mean difference (SMD) will be used for analysing the continuous data (eg, the index of serum markers of inflammation, IBDQ, BDI, Hamilton Anxiety Inventory (HAM-A), FACIT-FS). The WMD will be employed for the same scale or same evaluation instrument, and the SMD will be employed for applying the different scales and methods to counting the similar outcome variables.^{32 33}

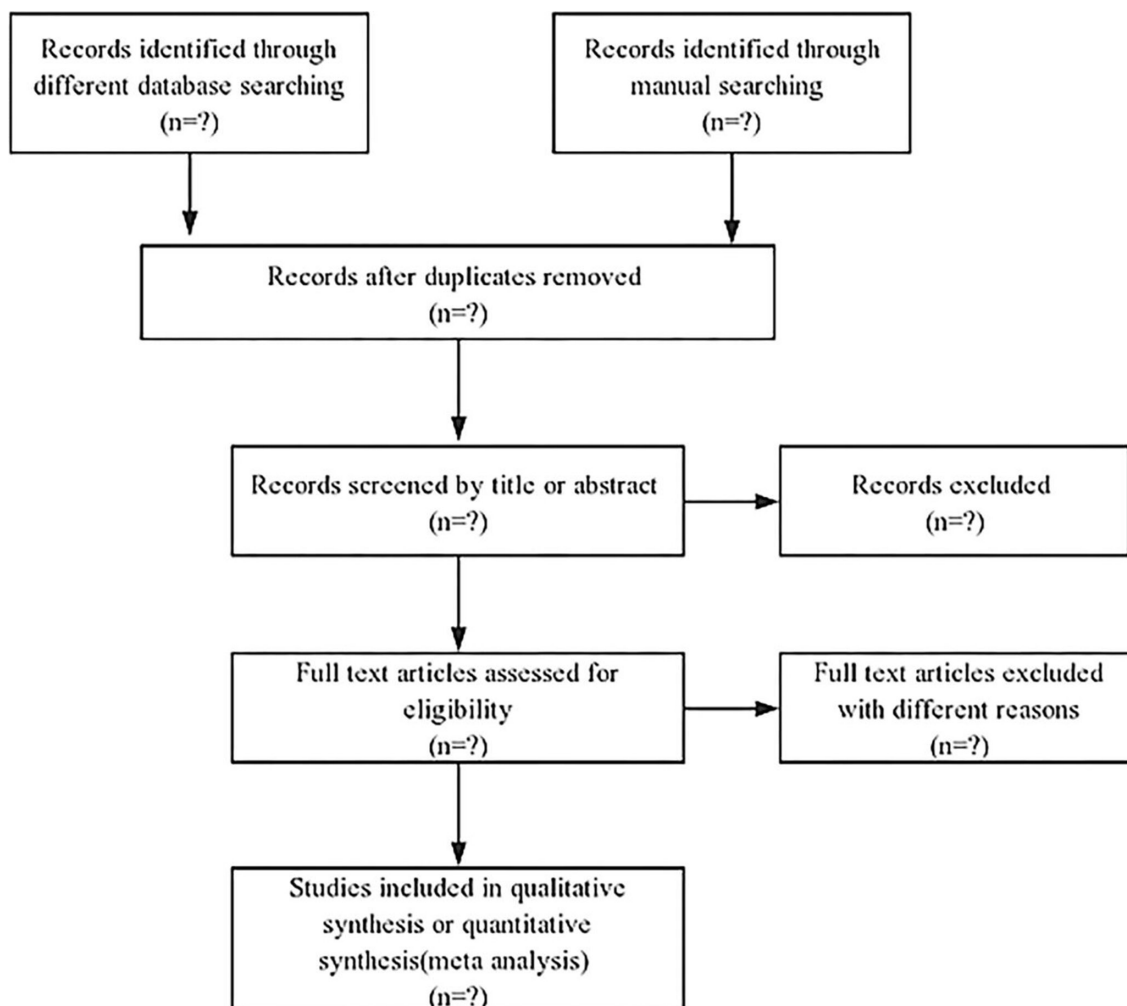


Figure 1 Flow diagram of the study selection process.

Unit of analysis issues

The unit of analysis will be based on the summarised outcome data on account of the lack of individual patient data.

Dealing with missing data

For the missing but necessary data, the corresponding author or coauthors of included studies will be asked for the missing data. Moreover, if possible, the influence of the missing data on the results will be assessed by using the sensitivity analysis. And the potential influence of missing data will be addressed in discussion.

Analysis of heterogeneity

The heterogeneity will be analysed by using χ^2 test to present the forest plot on RevMan V.5.3. Generally, $p < 0.1$ of the χ^2 test will be considered statistically significant according to the Cochrane Handbook.³⁴ Moreover, the statistical inconsistency will be assessed through calculating I^2 index. The I^2 value is classified as the following, 0%–40% no significance; 30%–60% moderate heterogeneity; 50%–90% massive heterogeneity and 75%–100% considerable heterogeneity.

Assessment for reporting biases

If there are more than ten included studies, a funnel plot will be used for analysing the potential reporting biases.

Data synthesis

Data synthesis for the inputted clinical data will be accomplished by the RevMan software (V.5.3). When the I^2 test shows little or low heterogeneity ($I^2 < 50\%$), the fixed-effects model will be employed for the pooled data. Otherwise, the random-effects model will be used when the I^2 value is 50%–75%. If there is considerable heterogeneity of included studies, meta-analysis will not be performed. However, subgroup analysis will be provided for the potential reasons of considerable heterogeneity.

Subgroup analysis and investigation of heterogeneity

If data of included studies are available, subgroup analysis will be implemented based on the factors that may influence the effect of intervention. The factors will include age, gender, the type of IBD (CD and UC), the type of acupuncture intervention (manual acupuncture, electroacupuncture, auricular acupuncture, scalp acupuncture, abdominal acupuncture, acupoint catgut

embedding, etc), the type of control (no treatment/waiting list, sham control or active treatment), the duration of follow-up (eg, short term (within 4 weeks), medium term (up to 12 weeks) and long term (more than 12 weeks). If necessary, the reasons of considerable heterogeneity will be further interpreted in discussion.

Sensitivity analysis

A sensitivity analysis will be performed to judge the robustness and reliability of the results according to the methodological weakness (eg, sequence generation and allocation concealment were not adequately conducted), sample size (eg, greater or less than 30 participants in each group) and missing data. The risk of bias will be further defined if the robustness is low of the sensitivity analysis. Moreover, the study with high or unclear risk of bias will be excluded from analysis.

Evaluating the quality of evidence

The quality of evidence for each result will be assessed independently by two reviewers using the Grading of Recommendation Assessment, Development and Evaluation (GRADE).³⁵ Moreover, it will also be classified into four categories in line with the GRADE rating standards: high, moderate, low or very low.^{35 36}

Involvement of patients and the public

No patients and the public are involved.

Ethics and dissemination

Ethical approval will not be needed in this review due to no data are involved in patient's information and privacy. The result will be published and diffused in a peer-reviewed journal or relative conferences.

DISCUSSION

More evidence will be provided in this meta-analysis to prove the effectiveness and safety of complementary and alternative therapies for IBD. The conclusion of this review may bring benefit to patients with IBD, clinicians and other relevant personnel. If the protocol is revised, the reasons of amendments will also be finally reported.

Contributors F-RL and R-RS designed the systematic review, the protocol is drafted by Y-FZ, NS, S-RC, X-GX and R-RS modified the manuscript. X-YY, X-DD, Y-ZQ, L-YH, X-GX, JZ, Y-FZ and NS participated in the work of search strategy, data extraction, data synthesis and analysis plan. In fact, the quality of review still is monitored by S-RC, Z-JL and R-RS. All authors read and approved the publication of this review.

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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.

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this is a protocol without data.

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