BMJ Open

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045090
Article Type:	Protocol
Date Submitted by the Author:	22-Sep-2020
Complete List of Authors:	zhou, yuanfang; Chengdu University of Traditional Chinese Medicine, acupuncture and tuina school Sun, Ning; Chengdu University of Traditional Chinese Medicine, Cheng, Shirui; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital; Chengdu University of Traditional Chinese Medicine, Acupuncture & Brain Science Research Center dong, deng; Chengdu University of Traditional Chinese Medicine yin, ye; Chengdu University of Traditional Chinese Medicine Li, Zhengjie; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School Zhou, Jun guixing, xu; Chengdu University of TCM, ; Qu, Yuzhu Huang, Liuyang Liang, Fan-rong; Chengdu University of Traditional Chinese Medicine, Acu-moxibustion and Tuina school Sun, Ruirui; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital; Chengdu University of Traditional Chinese Medicine, Acupuncture & Brain Science Research Center
Keywords:	Gastroenterology < INTERNAL MEDICINE, Inflammatory bowel disease < GASTROENTEROLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

Authors and Affiliations

Yuan-Fang Zhou,[†] Ning Sun,[†] Shi-Rui Cheng,[†] Xiao-Dong Deng, Xiang-Yin Ye, Zheng-Jie Li, Jun Zhou, Gui-Xing Xu, Yu-Zhu Qu, Liu-Yang Huang, Fan-Rong Liang,[*] Rui-Rui Sun[*]

Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China

[†]Co-first authors: Yuan-Fang Zhou, Ning Sun, Shi-Rui Cheng

*Co-corresponding authors: Rui-rui Sun, Fan-rong Liang

Correspondence to:

Rui-Rui Sun, Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China. Postal address: 37 Shierqiao Road, Chengdu, Sichuan, China. Telephone: +86 13882178547. Email: sunruirui@cdutcm.edu.cn

Fan-Rong Liang, Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China. Postal address: 37 Shierqiao Road, Chengdu, Sichuan, China. Telephone: +86 13608058216. Email: acuresearch@126.com

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

ABSTRACT

Introduction Previous reviews have suggested that the effectiveness of acupuncture therapy for inflammatory bowel disease (IBD) has not well been demonstrated due to the limited high quality randomized controlled trials (RCTs). In recent years, the growing research into acupuncture for IBD make it possible to conduct a further systematic review and synthesize 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 August 2020. RCTs comparing acupuncture with sham control, routine care, symptoms alleviation for managing IBD were 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 (V5.3) 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 for data of this review isn't involved in patient's information and privacy. The result will be published and diffused in a peer- reviewed journal or relative conferences.

Trial registration number CRD42020157903

Strengths and limitations of this study

- Previous reviews have suggested that more high-quality clinical trials are needed to demonstrate acupuncture effect on IBD. To prove the effectiveness and safety of acupuncture for IBD, this study will update data synthesis by including clinical trials published in recent decade.
- Evaluating the safety of acupuncture in the included trials helps provide evidence and indicate guideline for the application of acupuncture in the clinic.
- Since clinical trials may employ several different outcomes, a pooled analysis of all included studies may not be possible, then subgroup analyses will be used instead.

BACKGROUND

Inflammatory bowel disease (IBD) is a chronic intestinal disease characterized by abdominal pain, diarrhea and rectal bleeding.[1] It is mainly divided into crohn's

disease (CD) and ulcerative colitis (UC).[2] In western countries, the annual highest incidence of CD and UC is respectively estimated 29.3 and 57.9 per 100 000 people.[3] And the incidence of IBD in Asia is also gradually growing.[4,5] In addition, IBD patients are often accompanied by emotional disorders and malnutrition, which may result in high medical cost with financial burden and reduced work productivity.[6,7,8]

The management of IBD include drug management (5- aminosalicylic acid, prednisolone, corticosteroids,etc.), surgical treatment, nutritional support ,antibiotic therapy and lifestyle correction,.[9-12] However, drug management are found causing side effects such as renal toxity, hemorrhagic risk and headache , etc.[13-15] Vegetarian or gluten-free diets were not certified a relevant impact on the improvement of IBD, but was found significantly associated with lower psychological well-being in IBD patients.[16] Moreover, emergency surgeries and low pre-operative albumin level of UC patients may result in their poor survival.[17,18] Therefore, nonpharmacological interventions are 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 diarrhea .[21,22] In addition, Chen et al and Wen et al respectively pointed that acupuncture can improve diarrhea, hematochezia and abdominal pain of UC patients.[23,24] In addition, it is reported that acupuncture not only improves IBD patients' quality of life, but also prevent their fatigue.[25,26]

The mechanism of acupuncture treating for IBD may be related to the

modulation of intestinal flora,[27] immune system.[28-30] Meanwhile, imaging studies suggested that the effect of acupuncture may be related to the regulation of IBD patients' brain homeostatic afferent processing network .[31,32]

However, previous reviews have suggested that high-quality randomized controlled trials (RCTs) are limited to demonstrate the effectiveness of acupuncture therapy for inflammatory bowel disease (IBD).[33] With the increasing number of RCTs published in recent years, it's necessary to update recent published clinical RCTs and synthesize data, so as to seek more consistent findings of the effectiveness. Therefore, a systematic review and meta- analysis will be conducted on the available evidence to prove the clinical effectiveness and safety of acupuncture therapy.

METHODS

Criteria for included studies in this review

Type of studies

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

Type of participants

Trials on UC or CD patients 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 and scalp acupuncture 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) used the included studies, such as CD activity index (CDAI) and the Colitis activity index (CAI).

Secondary outcomes

(1) Quality of life using any validated scales.

(2) Symptoms of anxiety and depression measured by any validated screening scales.

(3) Fatigue measured using any validated scales.

(4) Adverse events caused by acupuncture.

Search methods for identifying the included studies

Electronic search

The following databases will be searched from inception to January 2020: Cochrane Library, MEDLINE, EMBASE, Ovid, the Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), the Chongqing Chinese Science and Technology Periodical Database (VIP) and Wanfang Database.

The RCTs that evaluates the effectiveness of acupuncture therapy for IBD by setting

comparators or controls mentioned abovewill be included. No restrictions on language of the included studies. The following medical search headings (MESH) will be searched: (1) inflammatory bowel disease, bowel disease inflammatory, colitis ulcerative, crohn disease; (2) acupuncture, acupuncture therapy, electroacupuncture, electroacupuncture therapy, manual acupuncture, acupoint; and (3) randomized controlled trial, randomized controlled, clinical trial. The search terms for MEDLINE is displayed in table 1. In addition, the same searching strategy in Chinese language 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 NIH clinical registry ClinicalTrials. gov (https://www. clinicaltrials. gov/), the International Clinical Trials 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. Firstly, 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. Then the full-text of qualified studies will be read. The potentially missing trials from the reference list will be also identified by the same two reviewers. Lastly, the final selected studies will be cross-verified by the other two reviewers (G-XX 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.

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 PICOS as following acquisition forms: studies' basic information (title, first author, corresponding author, authors' country, sponsor, journal and time for publishment), participants (sample size, sex,and age), details of intervention (kinds of intervention, acupoint selection, frequency of treatment) andcontrol(sham control, usual care and management for alleviating symptoms of IBD), outcomes (outcome measurements, adverse events, andthe follow-up). Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) will be used to check the data extraction of acupuncture techniques.[34] 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 tool for risk of bias will be used for included studies by two reviewers (Y-FZ and NS) respectively. [35] The assessment of risk of bias includes six main domains (random sequence generation, allocation concealment, blinding of participants 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 evaluated with low risk of bias shows severe heterogeneity on key domains, the trial will be double-checked to re-define 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 synthesized and statistically analyzed by using the RevMan V5.3. The relative risk (RR) with 95% Confidence Intervals (CIs) will be employed for analyzing the dichotomous data. Whereas, the 95% CIs with weighted mean difference (WMD) or a standard mean difference (SMD) will be used for analyzing the continuous data. The WMD will be employed for the same scale or same evaluation instrument, whereas, the SMD will be employed for different evaluation tools.[36]

Unit of analysis issues

If the units of each outcome used in different trials are different, they will be

transformed into the International System of Units for statistical analysis.

Dealing with missing data

For the missing but necessary data, the corresponding author or co-authors 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 analyzed by using $\chi 2$ test to present the forest plot on RevMan V5.3. Generally, $p<0.1$ of the $\chi 2$ test will be considered statistically significant according to the Cochrane Handbook.[37] Moreover, the statistical inconsistency will be quantitatively calculated though I^2 test. The I^2 value is classified as the following, 0%-40% no significance; 30%-60% moderate heterogeneity; 50%-90% massive heterogeneity; 75%-100% considerable heterogeneity.

Assessment for reporting biases

If there are more than ten included studies, a funnel plot will be used for analyzing 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 is available, subgroup analysis will be implemented based on the variations of characteristics such as age of participants, influential factors of diseases, sub-type of disease (CD and UC), types of acupuncture intervention and controls, sample size, etc. 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. Several items for evaluating thesensitivity such as methodological weakness, sample size and missing data will be considered. The risk of bias will be further defined if the robustness is low of the sensitivity 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).[38] Moreover, It will also be classified into four categories in line with the GRADE rating standards: high, moderate, low or very low.[39,40]

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 is 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 acupuncture therapy for IBD. The conclusion of this review may bring benefit to IBD patients , clinicians and other relevant personnel. If the protocol is revised, the reasons of amendments will also be finally reported.

Author Contributors F-RL and R-RS designed the systematic review, the protocol is drafted by Y-FZ, NS, S-RC. NS, S-RC, G-XX and R-RS modified the manuscript.

Y-XY, X-DD, Y-ZQ, L-YH, G-XX, 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 have read and approved the publication of this review.

Funding This study was supported by grants from the National Natural Science Foundation of China for the Youth (NO. 81904096), the major program of the National Natural Science Foundation of China (NO. 81590950, 81590951) and China Postdoctoral Science Foundation (NO. 2019M653361).

Competing interests none declared.

Patient consent not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017;11(1):3–25.
2. Gecse KB, Vermeire S. Differential diagnosis of inflammatory bowel disease: imitations and complications. Lancet Gastroenterol Hepatol. 2018;3(9):644–653.
3. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769–2778.
4. Windsor JW, Kaplan GG. Evolving Epidemiology of IBD. Curr Gastroenterol Rep. 2019;21(8):40. Published 2019 Jul 23.

5. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50(8):942-951.

6. Cao Q, Huang YH, Jiang M, Dai C. The prevalence and risk factors of psychological disorders, malnutrition and quality of life in IBD patients. Scand J Gastroenterol. 2019;54(12):1458-1466.

7. Shafer LA, Walker JR, Restall G, et al. Association Between IBD Disability and Reduced Work Productivity (Presenteeism): A Population-Based Study in Manitoba, Canada. Inflamm Bowel Dis. 2019;25(2):352–359.

8. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12(12):720–727.

9. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–s106.

10. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol. 2018;53(3):305–353.

11. Bischoff SC, Escher J, Hébuterne X, et al. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease [published online ahead of print, 2020 Jan 13]. Clin Nutr. 2020;S0261-5614(19)33128-0.

12. Elseviers MM, D'Haens G, Lerebours E, et al. Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy?. Clin Nephrol. 2004;61(2):83–89.

13. Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis. 2017;49(4):338–358.

14. Nielsen OH, Munck LK. Drug insight: aminosalicylates for the treatment of IBD. Nat Clin Pract Gastroenterol Hepatol. 2007;4(3):160–170.

15. Schreiner P, Yilmaz B, Rossel JB, et al. Vegetarian or gluten-free diets in patients with inflammatory bowel disease are associated with lower psychological well-being and a different gut microbiota, but no beneficial effects on the course of the disease. United European Gastroenterol J. 2019;7(6):767-781.

16. Ackermann C, Tondelli P. Entzündliche Darmerkrankungen (Morbus Crohn und Colitis ulcerosa): Möglichkeiten und Grenzen der chirurgischen Therapie [Inflammatory bowel diseases (Crohn disease and ulcerative colitis). Possibilities and limitations of surgical therapy]. Ther Umsch. 1991;48(7):471-479.

17. Lin CC, Wei SC, Lin BR, et al. A retrospective analysis of 20-year data of the surgical management of ulcerative colitis patients in Taiwan: a study of Taiwan Society of Inflammatory Bowel Disease. Intest Res. 2016;14(3):248-257.

18. Ji J, Lu Y, Liu H, et al. Acupuncture and moxibustion for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2013;2013:158352.

19. Stein DJ. Massage Acupuncture, Moxibustion, and Other Forms of Complementary and Alternative Medicine in Inflammatory Bowel Disease. Gastroenterol Clin North Am. 2017;46(4):875-880.

20. Lin Z, Wu H, Fu Y, Dai S. Application of Herbaceous Medications for Inflammatory Bowel Disease as a Complementary and Alternative Therapy. Inflamm Bowel Dis. 2019;25(12):1886-1895.

21. Bao CH, Zhao JM, Liu HR, et al. Randomized controlled trial: moxibustion and acupuncture for the treatment of Crohn's disease. World J Gastroenterol. 2014;20(31):11000-11011.

22. Bao C, Wu L, Wu H, et al. Active Crohn's Disease treated with acupuncture and moxibustion:a randomized controlled trial. Zhongguo Zhen Jiu. 2016;36(7):683-688.

23. Wen Y, Shi L, Li J, Du W, Chen Y, Lan X. Acupuncture Combined With Acupoint Catgut Embedding Sequential Therapy for Mild and Moderate Ulcerative Colitis. Zhongguo Zhen Jiu. 2018;38(4):353-357.

24. Chen K, Li C. Acupuncture Combined With Medication for Ulcerative Colitis With Damp-Heat Syndrome at Active Phase. Zhongguo Zhen Jiu. 2015;35(5):435-438.

25. Joos S, Wildau N, Kohnen R, et al. Acupuncture and moxibustion in the treatment of ulcerative colitis: a randomized controlled study. Scand J Gastroenterol. 2006;41(9):1056–1063.

26. Horta D, Lira A, Sanchez-Lloansi M, et al. A Prospective Pilot Randomized Study: Electroacupuncture vs. Sham Procedure for the Treatment of Fatigue in Patients With Quiescent Inflammatory Bowel Disease. Inflamm Bowel Dis. 2020;26(3):484–492.

27. Wei D, Xie L, Zhuang Z, et al. Gut Microbiota: A New Strategy to Study the Mechanism of Electroacupuncture and Moxibustion in Treating Ulcerative Colitis. Evid Based Complement Alternat Med. 2019;2019:9730176.

28. Sun J, Zhang H, Wang C, et al. Regulating the Balance of Th17/Treg via Electroacupuncture and Moxibustion: An Ulcerative Colitis Mice Model Based Study. Evid Based Complement Alternat Med. 2017;2017:7296353.

29. Wang CY, Zeng LL, Geng Y, et al. Effect of Electroacupuncture Stimulation of "Guanyuan" (CV 4) and "Zusanli" (ST 36) on Spleen Lymphocytes Treg/Th 17 Immune Balance in Ulcerative Colitis Mice. Zhen Ci Yan Jiu. 2016;41(1):55-59.

30. Zhao C, Bao C, Li J, et al. Moxibustion and Acupuncture Ameliorate Crohn's Disease by Regulating the Balance between Th17 and Treg Cells in the Intestinal Mucosa. Evid Based Complement Alternat Med. 2015;2015:938054.

31. Bao C, Wang D, Liu P, et al. Effect of Electro-Acupuncture and Moxibustion on

Brain Connectivity in Patients with Crohn's Disease: A Resting-State fMRI Study. Front Hum Neurosci. 2017;11:559.

32. Bao C, Liu P, Liu H, et al. Different brain responses to electro-acupuncture and moxibustion treatment in patients with Crohn's disease. Sci Rep. 2016;6:36636.

33. Ji J, Lu Y, Liu H, et al. Acupuncture and moxibustion for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2013;2013:158352.

34. Macpherson H, Altman DG, Hammerschlag R, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement. J Evid Based Med 2010; 3:140-155.

35. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

36. Yang M, Du T, Sun M, et al. Acupuncture for stable angina pectoris: a systematic review protocol. BMJ Open. 2018;8(4):e019798. Published 2018 Apr 4.

37. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library, 2008.

38. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.

39. Guyatt GH, Oxman AD, Vist GE, et al. Rating quality of evidence and strength of recommendations: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924.

40. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380–2.

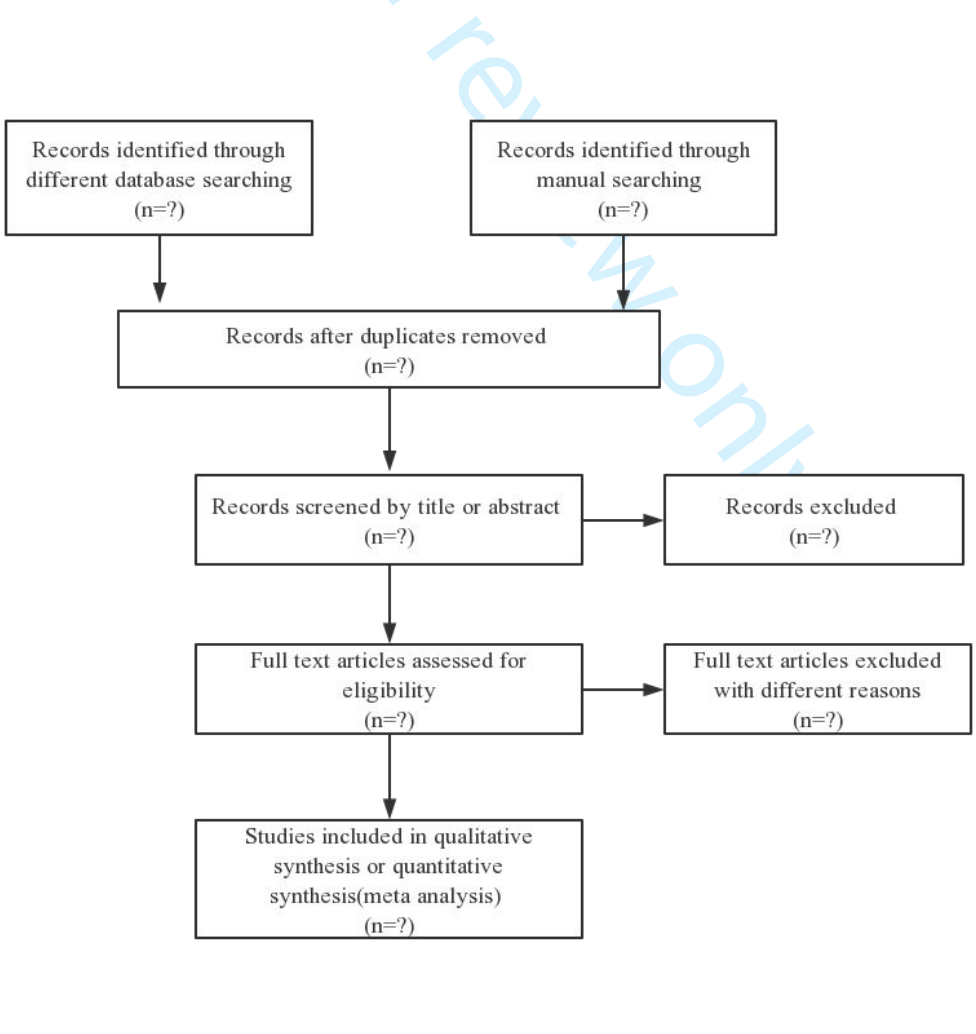
Table 1 Search strategy used in MEDLINE database

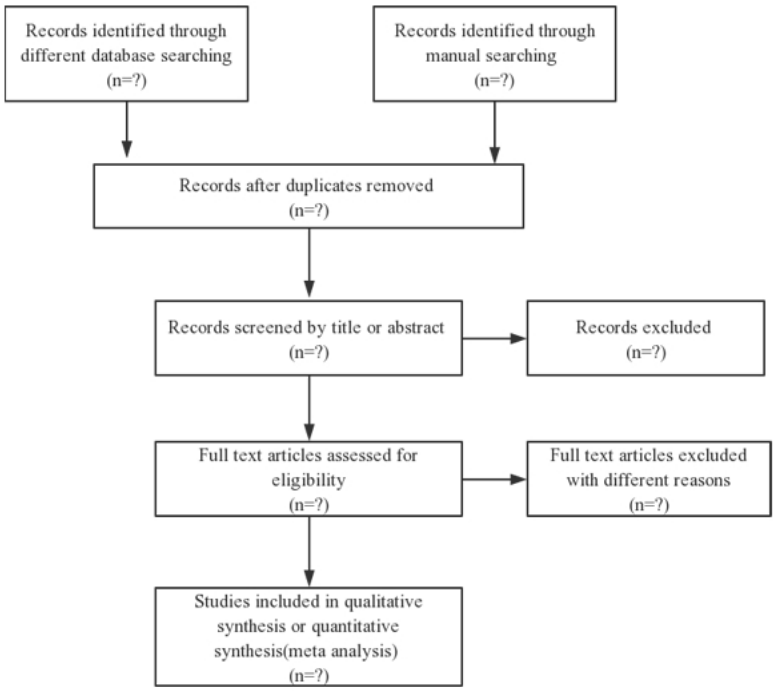
Figure 1 Flow diagram of the study selection process.

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 Ileitis, terminal or Ileitis, regional or ldiopathic proctocolitis or colitis gravis): ti,ab
#15	#11 or #12 or #13 or #14
#16	acupuncture therapy (MeSH)
#17	(acupuncture or body acupuncture or mamual acupuncture or electroacupuncture or electro-acupuncture or auricular acupuncture or scalp acupuncture or abdominal acupuncture or warm needling): ti,ab

#18	#16 or #17
#19	#10 and #15 and #18





63x53mm (300 x 300 DPI)

BMJ Open

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045090.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Apr-2021
Complete List of Authors:	zhou, yuanfang; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital Sun, Ning; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital Cheng, Shirui; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital; Chengdu University of Traditional Chinese Medicine, Acupuncture & Brain Science Research Center Deng, Xiaodong; Chengdu University of Traditional Chinese Medicine Ye, Xiangyin; Chengdu University of Traditional Chinese Medicine Li, Zhengjie; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital Zhou, Jun ; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School / The 3rd Teaching Hospital guixing, xu; Chengdu University of TCM, Acupuncture and Tuina School / The 3rd Teaching Hospital; Qu, Yuzhu ; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School / The 3rd Teaching Hospital Huang, Liuyang Sun, Ruirui; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School/The 3rd Teaching Hospital; Chengdu University of Traditional Chinese Medicine, Acupuncture & Brain Science Research Center Liang, Fan-rong; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School / The 3rd Teaching Hospital
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Complementary medicine, Gastroenterology and hepatology
Keywords:	Gastroenterology < INTERNAL MEDICINE, Inflammatory bowel disease < GASTROENTEROLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COMPLEMENTARY MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

Authors and Affiliations

Yuan-Fang Zhou[1†], Ning Sun[1†], Shi-Rui Cheng[1†], Xiao-Dong Deng[1], Xiang-Yin Ye[1], Zheng-Jie Li[1], Jun Zhou[1], Xu-Gui Xing[1], Yu-Zhu Qu[1], Liu-Yang Huang[1], Rui-Rui Sun[1*], Fan-Rong Liang[1*]

[1]Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China

[†]Co-first authors: Yuan-Fang Zhou, Ning Sun and Shi-Rui Cheng

*Co-corresponding authors: Fan-Rong Liang and Rui-Rui Sun

Correspondence to:

Professor Fan-Rong Liang, Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China. Postal address: 37 Shierqiao Road, Chengdu, Sichuan, China. Telephone: +86 13608058216. Email: acuresearch@126.com

Associate Professor Rui-Rui Sun, Acupuncture and Tuina School / The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China. Postal address: 37 Shierqiao Road, Chengdu, Sichuan, China. Telephone: +86 13882178547. Email: sunruirui@cdutcm.edu.cn

The effectiveness and safety of acupuncture therapy for inflammatory bowel disease: A protocol of systematic review and meta-analysis

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 randomized controlled trials (RCTs). In recent years, the growing research on acupucture for IBD make it possible to conduct a further systematic review and synthesize 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 (AMED), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), the Chongqing Chinese Science and Technology Periodical Database (VIP) 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 (V5.3) 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 is 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

Strengths and limitations of this study

- The synthesis of updated data helps provide more evidence of the effectiveness of acupuncture for IBD patients, 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 (CD and UC) would be a source of heterogeneity, which will be further explored in the subgroup analysis.

BACKGROUND

The Inflammatory bowel disease (IBD) is a chronic intestinal disease characterized by the abdominal pain, diarrhea 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, IBD patients are often accompanied by

emotional disorders and malnutrition, which may result in high medical cost with financial burden and reduced work productivity.[8-10]

The management of IBD include drug management (5-aminosalicylic acid, prednisolone, corticosteroids, etc.), surgical treatment, nutritional support, antibiotic therapy and lifestyle correction.[11-13] However, drug management are found causing side effects such as renal toxicity, hemorrhagic risk and headache, etc.[14-16] Moreover, emergency surgeries for the UC patients with low pre-operative 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 diarrhea.[21,22] Chen et al and Wen et al have also found the similar improvement on these symptoms of UC patients.[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 randomized 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 synthesize 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, semi-random 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 IBD, UC or CD patients 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 (CDAI) and the Colitis activity index (CAI).

Secondary outcomes

(1) Patients' quality of life, measured by the Inflammatory bowel disease 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 (BAI) 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, hematoma, syncope, etc.

Besides, objective indicators such as the serum concentrations of α1- 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 (AMED), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), the Chongqing Chinese Science and Technology Periodical Database (VIP) 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 (MESH) will be searched: (1) inflammatory bowel disease, bowel disease inflammatory, colitis ulcerative, Crohn's disease; (2) acupuncture, acupuncture therapy, electroacupuncture, electroacupuncture therapy, manual acupuncture, auricular acupuncture, scalp acupuncture, abdominal acupuncture, acupoint, acupoint catgut embedding; (3) randomized controlled trial, randomized 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 NIH clinical registry ClinicalTrials.gov (https://www.clinicaltrials.gov/), the International Clinical Trials 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. Firstly, 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. Secondly, 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 (G-XX 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 PICOS as following acquisition forms: studies' basic information (title, first author, corresponding author, authors' country, sponsor, journal and time for publishment), 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 (STRICTA) 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 re-define 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 synthesized and statistically analyzed by using the RevMan V5.3. The relative risk (RR) with 95% Confidence Intervals (CIs) will be employed for analyzing 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 analyzing the continuous data (eg. the index of serum markers of inflammation, IBDQ, BDI, 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]

Unit of analysis issues

The unit of analysis will be based on the summarized 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 co-authors 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 analyzed by using $\chi 2$ test to present the forest plot on RevMan V5.3. Generally, $p<0.1$ of the $\chi 2$ test will be considered statistically significant according to the Cochrane Handbook.[34] Moreover, the statistical inconsistency will be assessed though 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; 75%-100% considerable heterogeneity.

Assessment for reporting biases

If there are more than ten included studies, a funnel plot will be used for analyzing 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 is 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 four weeks), medium term (up to twelve weeks) and long term (more than twelve 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.[36,37]

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 is 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 IBD patients, clinicians and other relevant personnel. If the protocol is revised, the reasons of amendments will also be finally reported.

Author Contributors F-RL and R-RS designed the systematic review, the protocol is drafted by Y-FZ. NS, S-RC, G-XX and R-RS modified the manuscript. Y-XY, X-DD, Y-ZQ, L-YH, G-XX, 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 have read and approved the publication of this review.

Funding

This study was supported by grants from the National Natural Science Foundation of China for the Youth (NO. 81904096), the Department of Science and Technology in Sichuan Province for key research and development (2019YFS0081), Special Project of "Central Government Guides Local Science and Technology Development" in Sichuan Provincial Department of Science and Technology (2020ZYD046) and China Postdoctoral Science Foundation (NO.2019M653361).

Competing interests none declared.

Patient consent not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017;11(1):3–25.
2. Gecse KB, Vermeire S. Differential diagnosis of inflammatory bowel disease: imitations and complications. Lancet Gastroenterol Hepatol. 2018;3(9):644–653.
3. Büsch K, Ludvigsson JF, Ekström-Smedby K, Ekbom A, Askling J, Neovius M. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. Aliment Pharmacol Ther. 2014;39(1):57-68.
4. Lucendo AJ, Hervías D, Roncero Ó, et al. Epidemiology and temporal trends (2000-2012) of inflammatory bowel disease in adult patients in a central region of Spain. Eur J Gastroenterol Hepatol. 2014;26(12):1399-1407.
5. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease [published correction appears in Gastroenterology. 2017 Jun;152(8):2084]. Gastroenterology. 2017;152(2):313-321.e2.
6. Windsor JW, Kaplan GG. Evolving Epidemiology of IBD. Curr Gastroenterol Rep. 2019;21(8):40. Published 2019 Jul 23.
7. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50(8):942-951.
8. Cao Q, Huang YH, Jiang M, Dai C. The prevalence and risk factors of psychological disorders, malnutrition and quality of life in IBD patients. Scand J

Gastroenterol. 2019;54(12):1458-1466.

9. Shafer LA, Walker JR, Restall G, et al. Association Between IBD Disability and Reduced Work Productivity (Presenteeism): A Population-Based Study in Manitoba, Canada. Inflamm Bowel Dis. 2019;25(2):352–359.

10. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12(12):720–727.

11. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–s106.

12. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol. 2018;53(3):305–353.

13. Bischoff SC, Escher J, Hébuterne X, et al. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease [published online ahead of print, 2020 Jan 13]. Clin Nutr. 2020;S0261-5614(19)33128-0.

14. Elseviers MM, D'Haens G, Lerebours E, et al. Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy?. Clin Nephrol. 2004;61(2):83–89.

15. Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis. 2017;49(4):338–358.

16. Nielsen OH, Munck LK. Drug insight: aminosalicylates for the treatment of IBD. Nat Clin Pract Gastroenterol Hepatol. 2007;4(3):160–170.

17. Ackermann C, Tondelli P. Entzündliche Darmerkrankungen (Morbus Crohn und Colitis ulcerosa): Möglichkeiten und Grenzen der chirurgischen Therapie

[Inflammatory bowel diseases (Crohn disease and ulcerative colitis). Possibilities and limitations of surgical therapy]. Ther Umsch. 1991;48(7):471-479.

18. Lin CC, Wei SC, Lin BR, et al. A retrospective analysis of 20-year data of the surgical management of ulcerative colitis patients in Taiwan: a study of Taiwan Society of Inflammatory Bowel Disease. Intest Res. 2016;14(3):248-257.

19. Stein DJ. Massage Acupuncture, Moxibustion, and Other Forms of Complementary and Alternative Medicine in Inflammatory Bowel Disease. Gastroenterol Clin North Am. 2017;46(4):875-880.

20. Lin Z, Wu H, Fu Y, Dai S. Application of Herbaceous Medications for Inflammatory Bowel Disease as a Complementary and Alternative Therapy. Inflamm Bowel Dis. 2019;25(12):1886-1895.

21. Bao CH, Zhao JM, Liu HR, et al. Randomized controlled trial: moxibustion and acupuncture for the treatment of Crohn's disease. World J Gastroenterol. 2014;20(31):11000-11011.

22. Bao C, Wu L, Wu H, et al. Active Crohn's Disease treated with acupuncture and moxibustion:a randomized controlled trial. Zhongguo Zhen Jiu. 2016;36(7):683-688.

23. Wen Y, Shi L, Li J, Du W, Chen Y, Lan X. Acupuncture Combined With Acupoint Catgut Embedding Sequential Therapy for Mild and Moderate Ulcerative Colitis. Zhongguo Zhen Jiu. 2018;38(4):353-357.

24. Chen K, Li C. Acupuncture Combined With Medication for Ulcerative Colitis With Damp-Heat Syndrome at Active Phase. Zhongguo Zhen Jiu. 2015;35(5):435-438.

25. Joos S, Wildau N, Kohnen R, et al. Acupuncture and moxibustion in the treatment of ulcerative colitis: a randomized controlled study. Scand J

Gastroenterol. 2006;41(9):1056–1063.

26. Horta D, Lira A, Sanchez-Lloansi M, et al. A Prospective Pilot Randomized Study: Electroacupuncture vs. Sham Procedure for the Treatment of Fatigue in Patients With Quiescent Inflammatory Bowel Disease. Inflamm Bowel Dis. 2020;26(3):484–492.

27. Ji J, Lu Y, Liu H, et al. Acupuncture and moxibustion for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2013;2013:158352.

28. Macpherson H, Altman DG, Hammerschlag R, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement. J Evid Based Med 2010; 3:140-155.

29. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

30. He Y, Guo X, May BH, et al. Clinical Evidence for Association of Acupuncture and Acupressure With Improved Cancer Pain: A Systematic Review and Meta-Analysis. JAMA Oncol. 2020;6(2):271-278.

31. Mu J, Furlan AD, Lam WY, Hsu MY, Ning Z, Lao L. Acupuncture for chronic nonspecific low back pain. Cochrane Database Syst Rev. 2020;12:CD013814.

32. Crowther M, Lim W, Crowther MA. Systematic review and meta-analysis methodology. Blood. 2010;116(17):3140-3146.

33. Khan S, Memon B, Memon MA. Meta-analysis: a critical appraisal of the methodology, benefits and drawbacks. Br J Hosp Med (Lond). 2019;80(11):636-641.

34. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library, 2008.

35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.

36. Guyatt GH, Oxman AD, Vist GE, et al. Rating quality of evidence and strength of recommendations: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924.

37. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380–2.

Table 1 Search strategy used in MEDLINE database

Figure 1 Flow diagram of the study selection process.

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 Ileitis, terminal or Ileitis, regional or ldiopathic proctocolitis or colitis gravis): ti,ab
#15	#11 or #12 or #13 or #14

#16	acupuncture therapy (MeSH)
#17	(acupuncture or body acupuncture or mamual 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

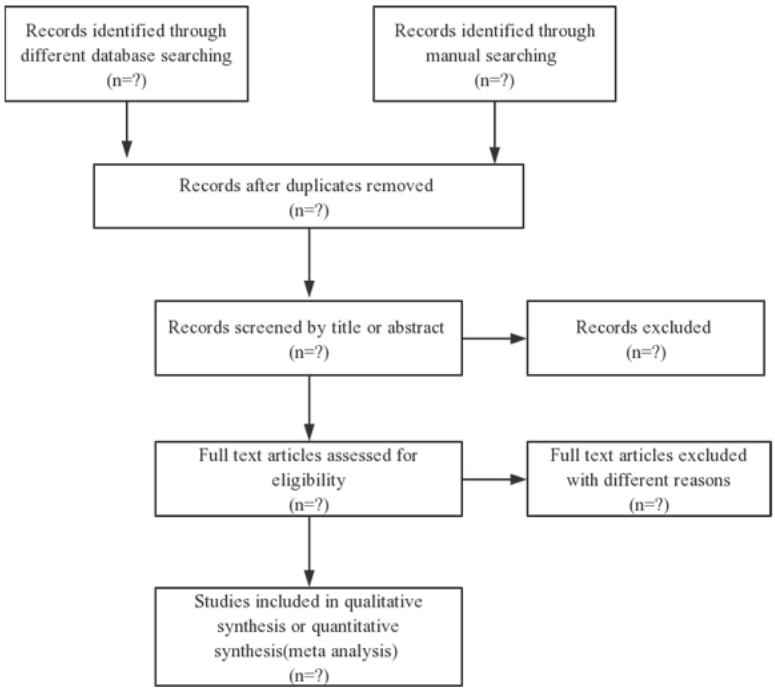


Figure 1 Flow diagram of the study selection process.

63x53mm (300 x 300 DPI)

e

3

4

1-2

15

15

4-5

5

6-8

8-9

8-9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.