INPLASY PROTOCOL

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None declared.

The Efficacy and Safety of Acupuncture-related Therapies in Treating Ulcerative Colitis: A protocol for systematic review and network meta-analysis

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Review question / Objective: **Ulcerative colitis (UC), a non-specific intestinal inflammatory disease of unknown cause, is characterized by abdominal pain, diarrhea, bloody purulent stool, and tenesmus. Acupuncture-related therapies have been used extensively in the treatment of UC, especially in China, and the results are promising but varying. Therefore, the purpose of this study is to compare the efficacy and safety of various acupuncture-related therapies in treating UC. Ulcerative colitis, a non-specific intestinal inflammatory disease of unknown cause, is characterized by abdominal pain, diarrhea, bloody purulent stool, and tenesmus. Acupuncture-related therapies have been used extensively in the treatment of UC in China, and the results are promising but varying. Therefore, the purpose of this study is to compare the efficacy and safety of various acupuncture-related therapies in treating UC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2022 and was last updated on 10 November 2022 (registration number INPLASY202230102).

INTRODUCTION

Review question / Objective: **Ulcerative colitis (UC), a non-specific intestinal inflammatory disease of unknown cause, is characterized by abdominal pain, diarrhea, bloody purulent stool, and tenesmus. Acupuncture-related therapies have been used extensively in the treatment of UC, especially in China, and the results are promising but varying. Therefore, the purpose of this study is to compare the efficacy and safety of various acupuncture-related therapies in treating UC. Ulcerative**

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Condition being studied: The Acupuncture-related Therapies; Ulcerative Colitis.

METHODS

Participant or population: The patients diagnosed with UC by a clear and widely recognized criterion will be recruited, and regardless of age, gender, race, nationality.

Intervention: For the experimental groups, acupuncture-related therapies (i.e. acupoint-based therapies, including manual acupuncture, electroacupuncture, warm acupuncture, acupoint embedding, acupoint injection, acupoint moxibustion) or their combinations with conventional therapies should be applied in the experimental groups, and regardless of differences in acupuncture techniques, acupoints prescription, and the duration or frequency of treatments.

Comparator: For the control groups, acupuncture-related therapies should not be used in the control groups, conversely, non-surgical conventional therapies (e.g. aminosalicylic acid, immunosuppressive agents, glucocorticoid, biological agents) or blank control methods (e.g. placebo, sham acupuncture) will be allowed.

Study designs to be included: Only randomized controlled trials (RCTs) of testing acupuncture-related therapies for UC will be eligible for our study without any limitation of population characteristics or languages. Non-RCTs such as clinical experience, system reviews, meeting abstracts, case reports, and animal trials will be eliminated. In addition to this, the adequacy of the original data is also essential.

Eligibility criteria: (1) Types of studies: only randomized controlled trials (RCTs) of testing acupuncture-related therapies for UC will be eligible for our study without any limitation of population characteristics or languages. Non-RCTs such as clinical experience, system reviews, meeting abstracts, case reports, and animal trials will be eliminated. In addition to this, the adequacy of the original data is also essential. (2) Types of participants: the patients diagnosed with UC by a clear and widely recognized criterion will be recruited, and regardless of age, gender, race, nationality. (3) Types of interventions: for the experimental groups, acupuncture-related therapies (i.e. acupoint-based therapies, including manual acupuncture, electroacupuncture, warm acupuncture, acupoint embedding, acupoint injection, acupoint moxibustion) or their combinations with conventional therapies should be applied in the experimental groups, and regardless of differences in acupuncture techniques, acupoints prescription, and the duration or frequency of treatments. For the control groups, acupuncture-related therapies should not be used in the control groups, conversely, non-surgical conventional therapies (e.g. aminosalicylic acid, immunosuppressive agents, glucocorticoid, biological agents) or blank control methods (e.g. placebo, sham acupuncture) will be allowed. (4) Types of outcomes: the primary outcomes of this NMA will be measured by ulcerative colitis endoscopic severity score (UCEIS)and total effective rate. Additionally, the amelioration of clinical symptoms, which include the severity of abdominal pain, diarrhea, bloody purulent stool or their number of occurrences, will also be taken into consideration. Besides, the quality of life of patients with UC and safety assessments, such as adverse events related to acupuncture, drop-out cases, will be regarded as secondary outcomes.

Information sources: A thorough search of potentially relevant literature will be conducted in 8 online databases from their

inception throughout March 2022: Web of Science, PubMed, EMBASE Database, the Cochrane Library, Chinese Scientific Journals Database (VIP), China Biological Medicine Database (CBM), Wan Fang databases and China National Knowledge Infrastructure (CNKI). Search strategy will be based on MeSH terms combining with free text words in English databases, while counterpart terms in Chinese will be applied in Chinese databases. In addition, under the guidance of snowball strategy, the related references of included literature will also be screened carefully without language restrictions. We will contact the corresponding author if the information we need is incomplete, and an intention-to-treat (ITT) analysis will also be used for missing or unreachable data.

Main outcome(s): The main outcomes of this NMA will be measured by ulcerative colitis endoscopic severity score (UCEIS)and total effective rate. Additionally, the amelioration of clinical symptoms, which include the severity of abdominal pain, diarrhea, bloody purulent stool or their number of occurrences, will also be taken into consideration.

Additional outcome(s): Besides, the quality of life of patients with UC and safety assessments, such as adverse events related to acupuncture, drop-out cases, will be regarded as additional outcomes.

Data management: Firstly, the retrieved literature will be imported into EndNote X8 to remove duplicates automatically, then primary screening will be performed independently by two reviewers according to the titles and abstracts. The studies not meeting the inclusion criteria will be excluded directly. Secondly, full texts will be browsed by the same two reviewers to select eligible studies, while the exclusion reasons will be recorded separately. Thirdly, a cross-checked of the results will be carried out to ensure the consistency of the screening. In the event of disagreement, a third senior assessor will be asked to assist in making the final judgement. After completing the literature selection, a data extraction table, which mainly includes first author's name, nationality, publication year, participants' characteristics (sample size, gender, mean age, extent of UC, duration of UC, and so on), interventions, comparators, outcomes , and methodological design will be established in Microsoft Excel 2016 in light of recommendations in the Cochrane Handbook.

Quality assessment / Risk of bias analysis: Two experienced researchers will independently assess the bias risk of all included studies under the guidance of the Cochrane Collaboration tool, which consisted of the following aspects: random sequence generation, assignment concealment, blinding of outcome assessors, blinding of participants and personnel, the integrity of outcome data, selective reporting, and other sources of bias. Each field has been classified as low risk, high risk, or unclear risk. Any disagreements will be resolved through discussion with the third senior assessor.

Strategy of data synthesis: Firstly, a pairwise meta-analysis will be conducted using Revman 5.3. (Cochrane Collaboration, Oxford, UK) for the direct comparisons. Secondly, considering the anticipated heterogeneity, the NMA within the Bayesian framework will be performed by WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) based on a random effect model for the results of the indirect comparisons. In addition, models will be calculated with Markov chain Monte Carlo algorithm (MCMC): 4 chains will be employed for simulation analysis, the step size will be set to 10, the number of annealing times will be set to 20,000 for reducing the impact on arbitrary values, and the number of iterations will be set to 50,000. The continuous outcomes will be measured by standard mean difference (SMD) with 95% confidence interval (CI) for indirect comparisons, while binary variable selection relative risk (RR) and 95% CI. Thirdly, the plot of surface under the cumulative ranking curve (SUCRA) will be calculated by STATA 14.0. (Stata Corporation, College Station, Texas, USA) to predict the potential ranking order.

Subgroup analysis: When significant heterogeneity is identified, subgroup analysis will be conducted in accordance with the potential sources of heterogeneity, for instance, the extent of UC, the duration of UC, as well as the site of lesion.

Sensitivity analysis: Given that varying levels of the methodological quality of studies may affect our results, sensitivity analysis will be conducted to assess the robustness of the results by eliminating high-risk studies.

Language: This NMA will be conducted without language restrictions.

Country(ies) involved: China.

Keywords: acupuncture, ulcerative colitis, systematic review, network meta-analysis, protocol.

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