INPLASY PROTOCOL

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None declared.

Is acupuncture an effective and safe complementary or alternative therapy for ulcerative colitis? A meta-analysis of randomized controlled trials

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Review question / Objective: **This study focused on whether acupuncture (MA/EA) can improve the therapeutic effect of medicine for ulcerative colitis and reduce adverse reactions, providing theoretical basis for acupuncture as an complementary and alternative medicine (CAM) for UC.**
Condition being studied: **Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease of the colonic mucosa that cause a lifetime of illness. Easy recurrence and refractory , which brings huge burden to patients' work, life, spirit and psychology, are the main characteristics of UC. Acupuncture may be an effective treatment for UC, so more and more patients are receiving it. However, whether acupuncture (manual acupuncture (MA)/ electroacupuncture (EA)) is more advantageous than medicine needs further discussion. This study focused on whether acupuncture (MA/EA) can improve the therapeutic effect of medicine for ulcerative colitis and reduce adverse reactions, providing theoretical basis for acupuncture as an complementary and alternative medicine (CAM) for UC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 September 2021 and was last updated on 15 September 2021 (registration number INPLASY202190041).

INTRODUCTION

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METHODS

Search strategy: We search from four English electronic databases (PubMed, Cochrane, Web of Science, EMBASE) and two Chinese electronic databases (China National Knowledge Infrastructure Database (CNKI) and Wanfang Database) . The search date is from the database construction to April 2021. The search strategy has three components: clinical status (UC), intervention (MA/EA), and study type (RCT). A combination of medical subject words (MeSH) and related free text words UC, manual acupuncture/ electroacupuncture, and randomized controlled trials. Resolve differences through negotiation and reach consensus. Furthermore, additional publications were identified through a manual search of previous published systematic reviews and the list of references to the included studies.

Participant or population: Participants were over 16 years old, with no limitation on gender and disease course, regardless of race, gender or region. Combined with the medical history, clinical features, physical examination and endoscopy, the diagnosis of UC was qualified under the guidance of relevant guidelines recognized in domestic and abroad.

Intervention: MA or EA (acupuncture needle model and manufacturer, acupuncture point, acupuncture intervention time, treatment frequency, treatment duration and stimulation method are not limited) single or combined drugs to manage UC.

Comparator: Oral drugs, single or combined, the same as the corresponding intervention group.

Study designs to be included: We chose randomized controlled trials.

Eligibility criteria: P: Participants were over 16 years old, with no limitation on gender and disease course, regardless of race, gender or region. Combined with the medical history, clinical features, physical examination and endoscopy, the diagnosis of UC was qualified under the guidance of relevant guidelines recognized in domestic and abroad. I: MA or EA (acupuncture needle model and manufacturer, acupuncture point, acupuncture intervention time, treatment frequency, treatment duration and stimulation method are not limited) single or combined drugs to manage UC.C: Oral drugs, single or combined, the same as the corresponding intervention group.O: The primary outcome was a reduction in clinical response rates and adverse drug reactions for UC at the end of the intervention period. The former is based on the total number of clinically effective people reporting UC, and the latter is based on the total number of adverse events, both of which were measured as dichotomies. Secondary outcomes included Baron scores, T-cell subsets

Information sources: We search from four English electronic databases (PubMed, Cochrane, Web of Science, EMBASE) and two Chinese electronic databases (China National Knowledge Infrastructure Database (CNKI) and Wanfang Database) . The search date is from the database construction to April 2021.

Main outcome(s): The main outcome was a reduction in therapeutic efficacy and adverse drug reactions for UC at the end of the intervention period. The former is based on the total number of clinically effective people reporting UC, and the

latter is based on the total number of adverse events, both of which were measured as dichotomies.

Additional outcome(s): Additional outcomes included Baron scores, T-cell subsets, inflammatory factors, and HADS scales, all measured as a continuous variable.

Data management: All authors of this study will receive professional training to understand not only the background of review and evaluation, but also the purpose and process. The literature retrieved through the search strategy is uniformly downloaded to EndNoteX9 for screening and integration. In this process, two authors of this paper will first read the titles and abstracts of the literature to remove duplicate literature. Then, they independently selected and recorded the titles, abstracts and keywords of the remaining papers, according to the established inclusion and exclusion criteria. At the same time, the standardized data extraction form was developed to extract the data independently. General information about included studies, including first author, year of publication, country, study design, sample size, detailed intervention, control treatment, course of disease, and duration of follow-up, was extracted. If the data is missing or unclear, the original author will be contacted by email to obtain the missing data. Researchers contacted the authors twice in a month, and if no response was received during that time, the data was classified as missing. In addition, any differences that arise during this process will be resolved through discussion between the two authors. If no agreement can be reached, the third makes the final choice to resolve the disagreement, who does not participate in literature screening and data extraction. If different articles with the same source of patients appeared, the literature with the most complete information and the longest follow-up period was selected. Basic information for included studies contains sample size, age and sex, diagnostic criteria, inclusion and exclusion criteria, detailed intervention, control treatment, etc. When there were multiple time points to choose after intervention, the end time of intervention was selected as the main data. Follow-up time points were used as secondary data and were divided into three groups: short, medium and long term. Short term is less than three months, medium term is three to six months, and long term is more than six months.

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias in the included literature based on the Cochrane Handbook v. 5.3.0 recommended Cochrane Risk of bias assessment tool and the Modified Jadad quality scale. The Cochrane Risk of bias assessment tool is divided into six categories: Random sequence generation (selection bias), Allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), Incomplete outcome data (attrition bias), Selective reporting (reporting bias)and Other bias. Risk grade is divided into low bias risk, unclear bias risk and high bias risk. The Modified Jadad quality scale includes the following four items: Randomization, Randomization concealment, Blinding method, Withdrawal and exit. A score of 1-3 indicates low quality and 4-7 indicates high quality. If a disagreement arises, a third author should be consulted to assist in adjudication.

Strategy of data synthesis: Data will be analyzed and consolidated using the Cochrane Collaboration's Review Manager 5.3 software and STATA 14.0. In the whole analysis process, a two-sided test was adopted, $p < 0.05$ was considered statistically significant[20, 21]. Relative Risk ratio (RR) and corresponding 95% Confidence interval (CI) were selected for dichotomous variables. For continuous variables, Weighted mean difference (WMD) was used to represent the corresponding 95%CI. According to the Cochrane Handbook, I 2 statistics were selected to test heterogeneity of the studies. When $P<0.1$, and $I2 \geq 50\%$, the heterogeneity of each study was large, and the random-

effects model was adopted. But if P<0.1, and I2<50%, there was some heterogeneity, and the fixed effect model was selected. Finally, when P≥0.1, and I2<50%, the studies were statistically homogeneous, and therefore fit the fixed-effects model.

Subgroup analysis: To evaluate the effects of different types of acupuncture (MA/EA), we performed a subgroup analysis of treatment effect, adverse effects, Baron score, type of intervention, while duration of intervention, frequency of treatment, duration of treatment, and type of medicine in the control group was also included.

Sensitivity analysis: We will explore the source of heterogeneity and the robustness of the assessment results through sensitivity analysis.

Language: Only English or Chinese study is allowed to be included.

Country(ies) involved: China.

Keywords: Ulcerative Colitis; acupuncture plus medicine; MA; EA; mesalazine; SASP; therapeutic efficacy; adverse drug reactions; meta-analysis.

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