Systematic Review and Meta-Analysis

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The effectiveness of acupoint herbal patching for functional constipation

Protocol for a meta-analysis and data mining

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Abstract

Background: Functional constipation is a common functional problem of the digestive system that has a negative impact on physical, mental health of patients and quality of life. At present, acupoint herbal patching as an adjuvant therapy is currently undergoing clinical trials in different medical centers. However, no relevant systematic review or meta-analysis has been designed to evaluate the effects of acupoint herbal patching on functional constipation. There is also a lack of systematic evaluation and analysis of acupoints and herbs.

Methods: We will search the following 8 databases from their inception to November 15, 2020, without language restrictions: the Cochrane Central Register of Controlled Trials, PubMed, Embase, the Web of Science, the Chinese Biomedical Literature Database, the Chinese Scientific Journal Database, the Wan-Fang Database and the China National Knowledge Infrastructure. The primary outcome measures will be clinical effective rate, functional outcomes, and quality of life. Data that meets the inclusion criteria will be extracted and analyzed using RevMan V.5.3 software. Two reviewers will evaluate the studies using the Cochrane Collaboration risk of bias tool. We will use the GRADE approach to assess the overall quality of evidence supporting the primary outcomes. We will also use Spass software (Version19.0) for complex network analysis to explore the potential core prescription of acupoint herbal patching for functional constipation.

Results: This study will analyze the clinical effective rate, functional outcomes, quality of life, improvement of clinical symptoms of functional constipation, and effective prescriptions of acupoint herbal patching for patients with functional constipation.

Conclusion: Our findings will provide evidence for the effectiveness and potential treatment prescriptions of acupoint herbal patching for patients with functional constipation.

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Abbreviations: AHP = acupoint herbal patching, CCS = cleveland clinic score, CI = confidence interval, CSBMs = complete spontaneous bowel movements, Development and Evaluation, FC = functional constipation, GRADE = Grading of Recommendations Assessment, PAC-QOL = Patient Assessment of Constipation Quality of Life Questionnaire, PAC-SYM = Patient Assessment of Constipation symptom, RCTs = randomized controlled trials, SP = P substances, VIP = vasoactive intestinal peptides.

Keywords: acupoint herbal patching, acupoint patch, complementary and alternative therapy, data mining, functional constipation, protocol, systematic review

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1. Introduction

Constipation is the most common functional problem of the digestive system, which may be secondary to diet, drugs, endocrine diseases, metabolic diseases, neurological diseases, psychiatric disorders or gastrointestinal obstruction.[1] When there is no secondary cause, constipation is diagnosed as functional constipation (FC). The Rome IV criteria classified FC as chronic constipation.[2] A survey study indicated that the most frequent symptoms of FC were decreased defecation frequency, difficulty in defecation, feeling of incomplete defecation and abdominal discomfort.[3] The incidence of FC is as high as 14% worldwide.[4]

At present, the treatment of the disease mainly includes conventional treatment, drug treatment, biofeedback treatment and surgical treatment, but the therapeutic effects vary and are often unsatisfactory.[5] Laxatives are commonly used as first-line pharmacological treatments as they are inexpensive and readily available over the counter. Nearly half of patients with severe constipation require a laxative.[6] Osmotic laxatives are typically well tolerated, but can cause dose-dependent side effects of bloating, flatulence and loose stools. Luminally acting prosecretory agents can be used as second-line treatments after standard laxatives. Those available for use in current clinical practice are Linaclotide, Plecanatide, and Lubiprostone.[2–7] However, diarrhea and nausea are the most common side effects. Anorectal biofeedback, transformational infection, nerve stimulation, colonial surgery and other treatments have brought significant economic burdens and thus considerable healthcare utilization to patients.[8–10] At the same time, FC seriously impairs the physical and mental health of patients and affects their quality of life [11]. Therefore, many people, including those who do not improve with existing medications or suffer many side effects, are interested in complementary and alternative medicine.

Acupoint herbal patching (AHP) is an ancient Chinese medicine method in which acupuncture points on the skin are manually stimulated with herbs. AHP is a treatment method to prevent diseases by strengthening the immune system through the stimulation of acupuncture points with a small amount of various herbal preparations.[12,13] Herbal patches are applied to acupoints, such as ST-25, ST-36 and RN-8, for 4 to 6 hours. The earliest record of AHP can be traced back to the classic "Prescriptions for Fifty two Diseases" (Wushier Bingfang) where AHP was listed as a treatment method, and it is still widely used today.[14,15] Modern studies suggest that AHP can regulate the level of related gastrointestinal regulatory peptides while improving colonic motility, thereby functioning in the treatment of digestive system diseases.[16] As a complementary and alternative therapy, AHP is often used to treat chronic functional diseases, and its application in FC has gradually become popular in recent years.[17] However, the clinical efficacy and potential treatment prescriptions of AHP for FC remain unclear, requiring further exploration. Therefore, a systematic evaluation of treatment outcomes and treatment prescriptions may help better explain and push this method into practice. In this study, we will investigate current evidence associated with the effectiveness and safety of AHP for FC, which will help clinicians to better use it in clinical practice.

2. Methods

2.1. Study type

We will collect randomized controlled trials (RCTs) to evaluate clinical effectiveness, functional outcomes, quality of life, and side effects of AHP on FC for systematic review and meta-analysis. RCTs comparing AHP for FC with no treatment, placebo, or conventional drugs (e.g., laxative agents) will be included. All eligible trials will be included regardless of language and publication type. RCTs that meet the requirements will be included for data mining. Articles of the following research types will be excluded: case series, observational studies (including cohort studies and case-control studies) and retrospective studies, qualitative studies, animal experiments, review articles. In addition, there will be no restrictions on study area, race, patient age and gender.

2.2. Participants

This review will include patients of any age who had been diagnosed with FC without limitations related to gender, race, study area, and education status. The diagnosis of functional constipation needs to be consistent with ROME II or III or IV. Participants were also included although ROME II or III or IV criteria were not mentioned, if they were diagnosed as constipated and were excluded for specific pathological cause, such as underlying structural or metabolic diseases.

2.3. Interventions

Participants in the intervention group are those undergoing acupoint herbal patching, regardless of herbal regimen, acupoints selected, patching time. There will not be any restrictions on age and original countries of the participants. In the control group, patients received medication, no treatment, sham or placebo acupoint catgut embedding, acupuncture/electro-acupuncture and etc. The other interventions between the control group and the intervention group should be the same.

2.4. Outcome measures

The primary outcomes will include complete spontaneous bowel movements (CSBMs), Cleveland Clinic Score (CCS), Patient Assessment of Constipation symptom (PAC-SYM), and clinical effective rate; The secondary outcomes will be Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL), adverse events and discontinuations due to adverse events.

2.5. Search strategy

An electronic search will be conducted. We will identify relevant studies from the Cochrane Central Register of Controlled Trials, PubMed, Embase, the Web of Science, the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (CSJD), the Wan-Fang Database (Wanfang) and the China National Knowledge Infrastructure (CNKI) from their inception to 15 July 2020. The search term will consist of 3 parts: intervention method, disease, and study type: ("acupoint application" or " acupoint sticker" or "crude herb moxibustion" or "medicinal vesiculation" or "herbal patch" or "herbal plaster" or "acupoint patch" or "Sanfu" or "acupoint sticking" or "point application therapy" or "drug acupoint application" or "winter diseases treated with acupoint stimulation in summer" or "drugs and points for point application in summer to treat the diseases with attacks in winter" or "acupuncture point application therapies" or "plaster therapy" or "external application therapy" or "acupoint herbal patching") and

("functional constipation" or "chronic functional constipation") and ("randomized controlled trial" or "randomized" or "case control studies" or "observational studies" or "case series" or "trial") and ("blind"). The details of the PubMed and Wan-Fang Database search strategies are provided in Tables 1 and 2. The similar but adaptive search strategies will be applied to other electronic databases. Language will be restricted to English and Chinese. Reference lists of relevant original studies will be screened to identify additional potentially citations. In addition, the following 3 trial registries will be searched for ongoing studies: Current Controlled Trials: www.controlled-trials.com; Clinical Trials: www.ClinicalTrials.gov; and Chinese Clinical Trial Registry: www.chictr.org.cn/index.aspx.

2.6. Study selection and data extraction

Author (Cao JZ) with experience in the field will guide the search. First, the NoteExpress 3.2.0 software (Available at: http://www.inoteexpress.com/aegean/) will be used to exclude duplicate references from different databases. Two review authors (Yan B, Jiang HL) will independently assess the title and abstracts of all citations found from the above search strategy. A copy of the full text article is obtained for the potentially eligible studies. These review authors will independently read the full text articles to include eligible studies; disagreement will be resolved by consensus through discussion with a third review author (Cao JZ). If conclusion still cannot be met, we will contact the author of the article to determine the eligibility of the study. The selection process will be showed in a PRISMA flow chart (http://www.prismastatementorg/) (Fig. 1). In the end, Two review authors (Yan B, Jiang HL) will extract data using a data extraction form according to the recommen dations of the Cochrane Handbook for Systematic Reviews of Interventions. the following data will be extracted: author, year of publication, country where the study was conducted, study period, original inclusion criteria, total number of people included in the study, acupoints, doses of herbs and time of application and etc.

2.7. Addressing missing data or unclear measurement scales

We will obtain the missing data or additional information by contacting the study authors via email or telephone if possible. Otherwise, we will analyze the available information and conduct sensitivity analysis to explore the potential impact of insufficient information on the results of the meta-analysis.

2.8. Risk of bias in included studies

Two review authors (Yan B, Liu XN) will independently evaluate each included study and will follow the domain-based evaluation as developed by the Cochrane Handbook for Systematic Reviews of Interventions. They will assess the following domains:

1. selection bias (random sequence generation and allocation concealment),
2. performance bias (blinding of participants and personnel),
3. detection bias (blinding of outcome assessment),
4. attrition bias (incomplete outcome data),
5. reporting bias (selective reporting),

Table 1

The search strategy for PubMed database.

Number	Search terms
#1	acupoint appliaction [MeSH]
#2	acupoint sticker [MeSH]
#3	crude herb moxibustion [MeSH]
#4	medicinal vesiculation [MeSH]
#5	herbal patch [MeSH]
#6	acupoint patch [MeSH]
#7	Sanfu [MeSH]
#8	acupoint sticking [MeSH]
#9	point application therapy [MeSH]
#10	drug acupoint application [MeSH]
#11	winter diseases treated with acupoint stimulation in summer [MeSH]
#12	drugs and points for point application in summer to treat the diseases with attacks in winter [MeSH]
#13	acupuncture point application therapies [MeSH]
#14	plaster therapy [MeSH]
#15	external application therapy [MeSH]
#16	complementary and alternative medicine [MeSH]
#17	complementary and alternative therapy [MeSH]
#18	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	functional constipation [MeSH]
#20	chronic functional constipation [MeSH]
#21	#19 or #20
#22	randomized controlled trial [MeSH]
#23	case control studies [MeSH]
#24	observational studies [MeSH]
#25	case series [MeSH]
#26	trial [MeSH]
#27	#22 or #23 or #24 or #25 or #26
#28	#18 and #21 and #27

Table 2

The search strategy for Wanfang database.

Number	Search terms
#1	acupoint appliaction [MeSH]
#2	acupoint sticker [MeSH]
#3	crude herb moxibustion [MeSH]
#4	medicinal vesiculation [MeSH]
#5	herbal patch [MeSH]
#6	acupoint patch [MeSH]
#7	Sanfu [MeSH]
#8	acupoint sticking [MeSH]
#9	point application therapy [MeSH]
#10	drug acupoint application [MeSH]
#11	winter diseases treated with acupoint stimulation in summer [MeSH]
#12	drugs and points for point application in summer to treat the diseases with attacks in winter [MeSH]
#13	acupuncture point application therapies [MeSH]
#14	plaster therapy [MeSH]
#15	external application therapy [MeSH]
#16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17	functional constipation [MeSH]
#18	chronic functional constipation [MeSH]
#19	#17 or #18
#20	randomized controlled trial [MeSH]
#21	case control studies [MeSH]
#22	observational studies [MeSH]
#23	case series [MeSH]
#24	trial [MeSH]
#25	#20 or #21 or #22 or #23 or #24
#26	#16 and #19 and #25

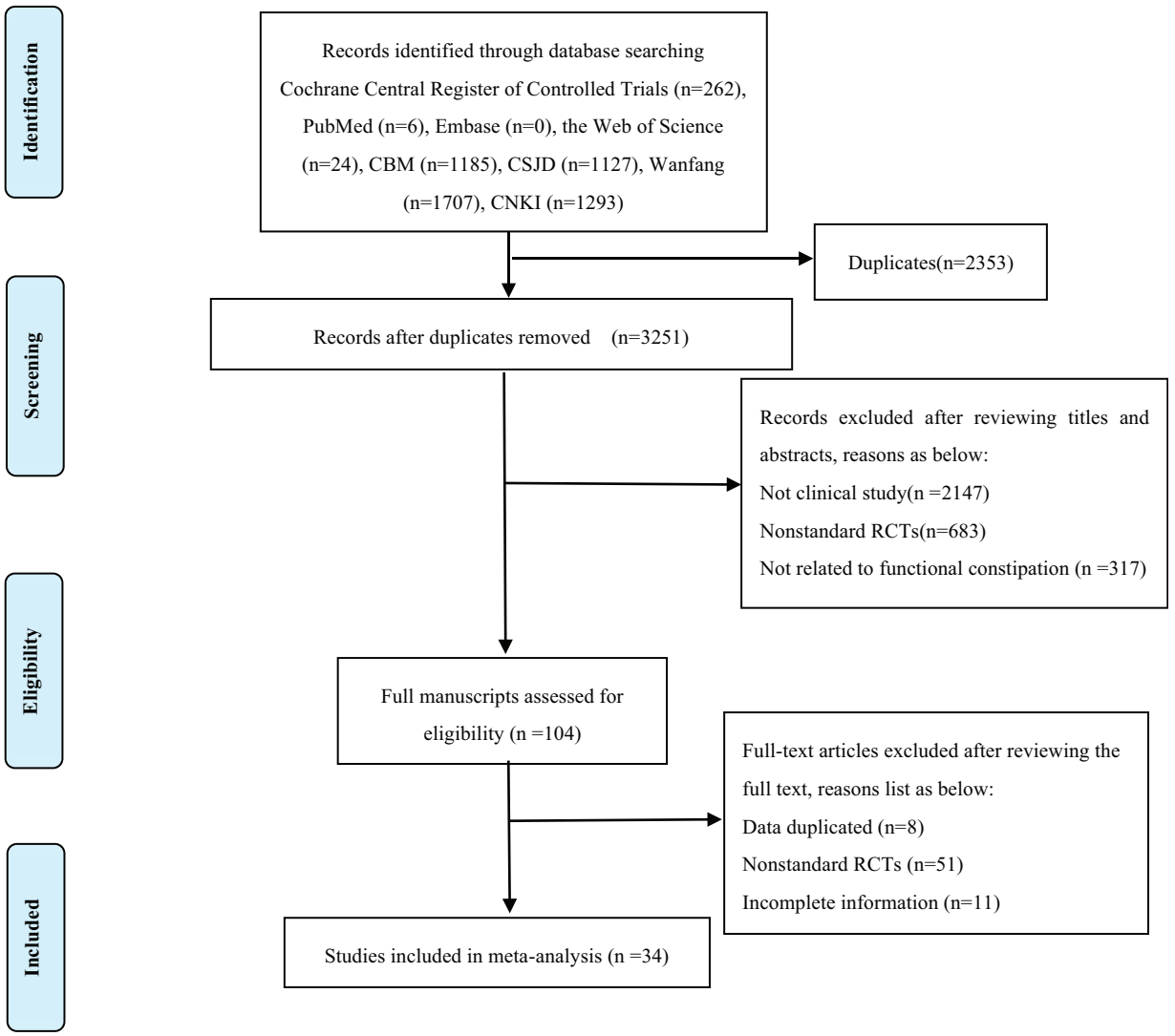

Figure 1. Flow chart of the search process.

6. other bias (such as pre-sample size estimation, early stop of trial).

Each domain will be divided into 3 categories: "low risk", "high risk", or "unclear risk".

2.9. Data synthesis and analysis

We will analyze the data with RevMan software (Version 5.3) (Available at: https://community.cochrane.org/help/tools-and-software/revman-5) provided by The Cochrane Collaboration.[18]A meta-analysis using random or fixed effects models will be conducted to summarize the data. Continuous data will be pooled and presented as mean differences or standardized mean difference with their 95% CI. Dichotomous data will be pooled and expressed as risk ratio with their 95% CI. We will interpret it using the following criteria: I^2 values of 25% is considered low levels of heterogeneity, 50% indicated moderate levels, and 75% indicated high levels.[19] Since low or moderate heterogeneity suggests little variability among these studies, the data will be analyzed in a fixed-effects model.[20] When significant heterogeneity occurs among the studies ($P < .05$, $I^2 > 50\%$), a random-effect model will be performed to analyze the data.

2.10. Additional analyses

Subgroup analysis will be conducted to evaluate the specific influence of intervention type, age, course of disease, treatment duration on pooled results. If the data is insufficient, qualitative synthesis will be conducted instead of quantitative synthesis. In addition, sensitivity analysis will be performed to examine the robustness of the results by eliminating low quality trials. We will also use Spass software (Version19.0) (Available at: https://www.ibm.com/analytics/spss-statistics-software) for complex network analysis to explore the potential core prescription of acupoint herbal patching for functional constipation.

2.11. Assessment of reporting biases

Reporting bias will be evaluated by visual inspection of Funnel plots. At the same time, Begg test and Egger test will be used to

test whether the funnel plot is symmetrical. A P value $< .05$ in Egger test or Begg test is considered statistically significant.

2.12. Confidence in cumulative evidence

In order to better prepare results for usage in guideline development, We will use the GRADE approach to assess the overall quality of evidence supporting the primary outcomes.[21] GRADE will be used to summarize the limitations in design, consistency, directness, precision, publication bias. The quality of each evidence will be divided into 4 levels: high, medium, low, and very low. Disagreements will be resolved by consensus.

3. Discussion

Constipation is used to describe symptoms related to difficulty in defecation. FC is a common functional problem of the digestive system. Long-term constipation can not only cause anxiety and depression, but also cause hemorrhoids and anal fissures, induce cardiovascular and cerebrovascular diseases, increase the risk of colorectal cancer, and even affect the quality of life of patients.[22] FC affects around 10% to 15% of the population.[23] Previous studies have confirmed that FC may be caused by colonic or anorectal dysmotility.[24]

At present, the treatment of FC varies from medical methods. Although lifestyle interventions and bulking agents help some patients with constipation, there is a lack of data to support their efficacy in those with chronic constipation. If empirical treatment for patients with chronic constipation fails, osmotic laxatives (e.g., lactulose and polyethylene glycol), serotonin (5-HT4) receptor agonists (e.g., tegaserod) or chloride channel activators (e.g., lubiprostone) can be considered. Osmotic laxatives, though effective in increasing stool frequency, are often associated with adverse reactions such as bloating and diarrhea, and typically do not effectively relieve the multiple symptoms of chronic constipation. Therefore, a number of patients with FC attempt to use complementary and alternative therapy, including AHP.[25,26] AHP is a herbal patch that is applied to specific acupoints to stimulate the skin, meridians, and collaterals to produce preventive and therapeutic effects. FC is the most common condition treated by AHP. A study has proved that traditional Chinese medicine can be absorbed from the skin.[27] Studies have also shown that after 4 to 6 hours, the transdermal absorption rate of herbs applied through herbal patches can reach 18.02% to 19.97%.[28] The herbal component of the patch contains free anthraquinones (aloe emodin, rhein, emodin, chrysophanol, physcion).[29] Pharmacodynamic studies have shown that free anthraquinone has a significant laxative effect.[30] In recent years, increasing researches have also demonstrated that herbal patches can regulate the expression levels of vasoactive intestinal peptide (VIP) and substance P (SP) and improve bowel function.[31,32]

Therefore, AHP is gradually applied to the treatment of FC. To the best of our knowledge, even though AHP is often used for fecal incontinence, there is no planned or published systematic review of the effectiveness and safety of AHP for FC. The purpose of this study is to evaluate the effect of AHP on clinical effectiveness, functional outcomes, quality of life, improvement of clinical symptoms of FC, adverse events, and drug withdrawal events in FC patients. In particular, we will analyze specific acupuncture points and herbal prescriptions used in FC with Spass software (Version19.0). Herein, this study will be the first to evaluate the clinical efficacy and effective prescription of AHP for FC patients, and may benefit practitioners in the field of complementary and alternative therapies.

4. Ethics and dissemination

Ethics approval is not required due to this work is carried out on published data. We aimed to explore the clinical effective rate, functional outcomes, quality of life, improvement of clinical symptoms of functional constipation, as well as effective prescriptions of AHP for patients with functional constipation. In the end, the results will be submitted to a peer-reviewed journal.

Author contributions

Yan B and Jiang HL had the original idea of this work and drafted the protocol. Cao JZ and Liu YZ designed the search strategies. Wang FC proposed some advice for the designand revision. Liu XN designed the flow chart. All authors critically revised the draft and approved the final manuscript.
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