Efficacy of Acupuncture in Subpopulations with Constipation: A protocol for a Systematic Review and Individual Patient data Meta-analysis

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Abstract

Background: Several systematic reviews have suggested that acupuncture is effective against constipation, but the factors predicting the effect of acupuncture in subpopulations with constipation are still unknown.

Methods: We will search six major English and Chinese electronic databases and two clinical trial registries from inception for randomized controlled trials that evaluate acupuncture for constipation. Two authors will independently identify the relevant studies, extract the information from the papers, and assess the risk of bias using the Cochrane RoB 2 tool. We will contact the primary researchers of the eligible trials for individual patient data (IPD). IPD from four trials are available from the China Academy of Chinese Medical Sciences CliniRsearch Data Management System. The primary outcomes are the change in weekly complete spontaneous bowel movements. IPD from the researchers will be standardized and harmonized. A one-stage approach will be used to synthesize the IPD. Our primary analysis will examine the efficacy of acupuncture in subpopulations with constipation using a general linear mixed model.

Discussion: This review will provide an IPD meta-analysis of acupuncture in constipation and demonstrate how the benefits of acupuncture may vary among subgroups of patients with constipation.

Systematic review registration: International Prospective Register of Systematic Reviews (Number: CRD42020188366)

Background

Chronic constipation is a functional bowel disorder resulting from colonic or anorectal dysfunction [1]. It is estimated that 14% of the global population is affected by constipation [2]. Although the symptoms associated with constipation are often intermittent and mild, they may be chronic, difficult to treat, and even debilitating [3]. The disease affects quality of life and results in a major social and economic burden [4].

The treatments for constipation include pharmacologic agents and lifestyle interventions. One common constipation treatment, dietary fibre, can improve stool frequency but not stool consistency, laxative use or painful defecation [5]; this treatment can also cause moderate gastrointestinal side effects [6]. Approximately half of patients were not completely satisfied with the current treatments, including laxatives and dietary fibre, mainly due to a lack of efficacy [7]. Acupuncture refers to a set of techniques in which practitioners stimulate specific points on the body. One multicentre, randomized, sham-controlled trial confirmed the short-term efficacy of acupuncture for constipation [8]. There are also several systematic reviews and meta-analyses based on aggregate patient data (APD) that evaluate acupuncture for constipation [9–11].

Reported risk factors for constipation include female sex (20.8% compared to 8.0% [12]); older age; high body mass index [13]; and lifestyle, including fibre and liquid intake as well as physical activity [13]. If only a specific subgroup of patients benefited from treatment, then targeting the entire constipated population might mask a significant benefit. Hence, we need to know which subgroup of patients benefit most from acupuncture therapy. Due to the limitation of APD and the sample sizes of individual trials, previous conventional meta-analyses of acupuncture for functional constipation have difficulty identifying the subgroups of individuals who may benefit most from acupuncture treatments [14–16]. IPD meta-analysis is the gold standard of systematic review, enabling more consistent identification and extraction of common individual-level characteristics, standardized outcome indicators, and greater statistical power for subgroup analysis [17].Therefore, this study was performed to synthesize clinical evidence with IPD meta-analysis for a subgroup analysis of the efficacy of acupuncture in different populations with chronic constipation.

Methods

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement (checklist in appdix) [18].

The China Academy of Chinese Medical Sciences (CACMS) ClinResearch Trialists' collaboration is a working group of researchers representing the clinicians, statisticians, and methodologists at the Clinical Evaluation Center of the China Academy of Chinese Medical Sciences. The perspectives of acupuncturists and clinicians involving the management of constipation are included in the design of the protocol. The collaboration also includes the primary investigators of the trials that provide the IPD.

The CACMS CliniRsearch Data Management System (available from http://118.144.35.11/wcr/) was established at CACMS to serve as the platform for clinical research data sharing and now contains the raw data of over 160 clinical trials supported by the Chinese government. We have already obtained the researchers' permission to obtain access to the IPD of four related trials [8, 19-21], for a total of 1782 IPD sets.

Criteria for considering studies for this review

Studies will be selected according to the following criteria.

Study type

We will include only randomized controlled trials (RCTs). To ensure the quality of the data, we will include only the RCTs that have a low risk of bias (RoB) in the randomization process, which means they are free of bias in random sequence generation and allocation concealment. Language will be restricted to English and Chinese. Unpublished data will be accepted if individual data were provided.

Patients

Eligible patients should have a diagnosis of functional constipation or chronic constipation. Rome II [22]/III [23]/IV [24] diagnostic criteria and other approved guidelines, such as ESNM 2019 (European Society of Neurogastroenterology and Motility) [25] and AGA(American Gastroenterological Association) [26], will also be accepted. Constipation secondary to another underlying disorder, such as medication, anatomical alterations, neurologic diseases, or metabolic disturbances, will be excluded. However, if some of the patients in a trial meet the criteria, we will still include the data from those specific patients in the IPD analysis.

Interventions

The main purpose of the eligible trials is to examine the effects of acupuncture, with or without baseline treatments, for constipation. Acupuncture refers to a family of procedures that stimulate anatomical locations on the body by a variety of techniques [27]. We will include only those treatments that were administered for at least 2 weeks. We will not limit the stimulation techniques, which could include needles, electricity, lasers, manual pressure, or other sources of stimulation. The baseline treatments may include lifestyle interventions, dietary suggestions, education and necessary laxative agents.

The control group should receive sham acupuncture or no acupuncture, with or without baseline treatments. Sham acupuncture is defined as any intervention designed to prevent the patients from knowing whether he or she has received real acupuncture. This includes needling at non-acupoints, non-penetrating needling or the use of placebo needles such as Streitberger and Kleinhenz [28] needles. Baseline treatments should be the same between the groups.

Outcomes

The primary outcomes are changes in weekly complete spontaneous bowel movements (CSBM). A spontaneous bowel movement (SBM) is defined as a bowel movement without the use of any medication or other methods to assist defecation in the previous 24 hours, and a CSBM is defined as an SBM associated with a sensation of complete evacuation [29]. Secondary outcomes include the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) [30], the Bristol Stool Form Scale, and general quality of life as measured by various instruments (such as the SF-36 and EQ-5D). For safety outcomes, we plan to document all adverse effects related to acupuncture and other treatment, and we are particularly interested in whether acupuncture can reduce the adverse events related to laxative agents and/or reduce their usage.

Search strategies

The following electronic databases will be searched from inception for potential studies: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, AMED (Allied and Alternative Medicine), the China National Knowledge Infrastructure (CNKI), and the China Biology Medicine disc (CBMdisc). Ongoing trials will be searched in the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. Free text and subject terms related to constipation and acupuncture will be used to develop systematic search strategies. The references of any identified meta-analyses will be screened as supplementary sources. We will also consult the key authors for additional literature and unpublished trials. The search strategies are listed in the appendix.

Data collection and data management

Selection of studies

All retrieved references will be imported to Endnote X9 for reference management. After the duplicate references are removed by the software, two independent investigators will select eligible studies among the remaining references by scanning the titles and abstracts according to the inclusion criteria. For each excluded reference, the reasons for exclusion will be given. Disagreements will be resolved by discussion.

Risk-of-bias assessment

All the included trials will be assessed by two independent investigators using the revised Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) [31]. The revised RoB tool assesses six domains of bias, comprising the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results and the overall bias. All the domains will be rated with either ‘low risk of bias’, ‘some concerns’, or ‘high risk of bias’ based on the signalling questions. Disagreements will be resolved by consensus. Considering that it is a challenge to conceal allocation from the patients or researchers in an acupuncture trial, only the trials with ‘low risk of bias’ in the randomization process and no ‘high risk of bias’ in any domain will be included.

Acquisition of the IPD

IPD from four trials are available from the CACMS CliniRsearch Data Management System. For the other trials, we will contact the corresponding authors of the included studies by E-mail to invite them to participate and provide the IPD. If there is no response from the authors after 2 weeks, we will send a reminder. We will send a maximum of three reminders to each author before marking the author as not responding. If there is no response, we will try to contact other authors of the trial. If none of the authors respond or one of the authors claim that the group is unwilling to share the data, the IPD of the study will marked unavailable. If the authors are willing to participate in our collaboration, they will also be invited

to be co-authors of the systematic review, and they will also be asked to share the relevant predictors and suggestion for the analysis. Any change from the protocol will be documented.

Patient-level data for each individual patient will include randomization data, randomization centre (for multicentre trials only), birth date, sex, baseline CSBM, nationality, job category, education background, occupation, BMI (body mass index), course of disease, information on compliance with acupuncture, colonoscopy results, routine stool examination results, baseline CSBMs, baseline Bristol score, PAC-QOL questionnaire results and additional outcomes.

Data management

If a researcher agrees to share data, we will sign a data share agreement. The raw data will be saved in their original format and then imported to R Core Team [32]. The data will be de-identified for patient privacy, and the remaining information will be saved in the RData format. R and the package 'dplyr' will be used for data manipulation. Each dataset will be reviewed for the completeness and clarity, and the data for each trial will be checked for consistency with the published reports. We will check for missing and duplicate data, search for unreasonable values with range checks, and identify the outlier data by an explanatory analysis. If individual patient-level data are missing, we will seek help from the original investigators. Any discrepancies will be documented, and we will contact the original investigators for help.

Data standardization

After data management, all data will be standardized and merged into a single database for the final analysis. The following tasks will be performed: renaming and labelling the variables, converting each variable to the appropriate data type (numeric, character or factor), manipulating the data frame to show one observation as one row and one variable per column, and standardizing different units to the same scale.

Statistical analysis plan

Study populations

All the analyses will be based on the intention-to-treat (ITT) principle, which means that the analysis will include all randomized patients, regardless of the treatment they actually received, whether they subsequently withdrew from treatment or whether there were any deviations from the protocol [33, 34].

Comparisons of baseline

Prior to the analysis of treatment outcomes, descriptive and exploratory analyses of baseline characteristics will be performed using all combined data to identify and show differences in baseline characteristics between two groups of trials. In general, statistical comparisons of means between groups will use t-tests, and ratios between groups to baseline will use the chi-squared test or Fisher's exact test.

Primary analysis

Definition of subpopulations

Our primary interest is not in the 'main effect' of treatment estimated across all the trials but rather the nature and degree of variation in the treatment effect according to predefined subpopulations. If enough data are available, the characteristics will be assessed as potential treatment effect modifiers. Individual patient-level characteristics that take into account whether the attributes of patients affect the outcome are as follows: (1) sex (female vs male); (2) age (toddlers (1-3 years); children (4-18 years), adults (19-59 years) and elders (≥ 60 years) [35-37]; (3) baseline constipation severity (serious (CSBMs≤2); not serious (CSBMs>2); (4) job category (mental work, physical work); (5) education background; and (6) BMI (BMI≥30 kg/m^2, BMI<30 kg/m^2). (7) Acupuncture characteristics, needling depth at ST25(depth≥20mm, depth<20 mm). These characteristics may be modified by consensus of the collaborators and any change will be documented.

Handling of missing data

Missing data for the primary endpoint and baseline covariates will be reported (%). If the missing data constitute less than 5% of the total dataset, we will generally discard the missing cases because these percentages usually have little impact on the outcome [38]. If the percentage of missing data for candidate covariates is between 5% and 60%, the missing data will be imputed by multiple imputation under the missing-at-random assumption [39]. If more than 60% of data are missing for the candidate covariate [40], the subgroup analysis for this factor will be abandoned.

Data analysis

The primary analysis will be conducted by a one-stage approach [41], which means that all IPDs are modelled simultaneously while accounting for the clustering of participants within studies. The IPD of the primary outcome will be synthesized by a generalized linear mixed model [42]. We anticipated that the treatment effect might be affected by interaction terms with treatment allocation. In this model, "trial" and "treatment * baseline characteristics" will be used as a random effect, and "treatment" will be used as a fixed effect. We will assess each interaction term between the treatment and the predefined subgroup factors and report the p-value. Two-way interaction tests will be regarded as nominally significant if the

two-sided p-value is less than 0.05. Finally, the primary researchers of the included original trials will be invited to provide useful insights into the analysis and the final interpretation of the results.

The quality of evidence for the main outcomes will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [43], and a summary of findings (SoF) table will be generated by the GRADEpro Guideline Development Tool (GRADEpro GDT, available from gradepro.org).

Analyses of secondary outcomes

The analyses of the secondary endpoints will be similar to the analysis of the primary outcomes.

Other prespecified analyses

Some acupuncturists claim that a subset of patients are good 'responders' to acupuncture therapy [44]; accordingly, we will attempt to identify the specific factors that might influence treatment. The subjects will be classified as 'good responders' (defined as a 50% or greater increase in CSBM from baseline) or 'non-responders (defined as less than a 50% increase in CSBM from baseline) according to the effect of treatment. Then, we will use multiple general linear regression, stratified by trial, to model the common linear dependence of the log odds of 'responder' status on patient characteristics including intervention (acupuncture vs sham acupuncture), age, baseline CSBMs, sex and interactions between intervention and these other baseline covariates.

Sensitivity analysis

Since compliance with acupuncture has an impact on treatment outcomes, we plan to perform sensitivity analysis by excluding patients with poor adherence to acupuncture (<80%), and any missing CSBM data will be imputed using the last observation carried forward (LOCF) method. In addition, because the different cutoff points of subgroups may lead to differences in results, the sensitivity analysis will be carried out by changing the subgroup cutoff points, such as changing the age classification to 10-year bins.

Publication bias

If the primary outcomes are available for sufficient numbers of included IPD and APD studies (n > 10), publication bias will be assessed by funnel plots and Egger's [45] test. Significant publication bias is defined as a p-value <0.1 on Egger's [45] test. If publication bias is detected, the trim-and-fill method will be used to correct for the asymmetry of the funnel plot and estimate the effect of publication bias [46].

Statistical software

All analyses will be conducted in R Core Team [32]. The 'lme4' and 'nlme' packages will be used for the one-stage IPD meta-analysis modelling, and the 'metafor' and 'ipdmeta' packages will be used for the two-stage IPD meta-analysis.

Role of the funding source

The funders will have no role in the study design, data collection, data analysis, data interpretation, or reporting. The corresponding author will have full access to all the data and will take responsibility for the decision to submit for publication.

Discussion

When synthesizing published aggregate data, it is difficult to explore the heterogeneity in estimates of the relative treatment effect. In this situation, it is important to identify the variation of the treatment effect across clinical subgroups. The use of published APD to investigate effect predictors is prone to bias because it cannot properly take patient-level characteristics into account for the analysis [47]. IPD meta-analysis is the most reliable and often the only way to investigate whether intervention effects vary by participant characteristics [48]. Additionally, acupuncture is a highly heterogeneous treatment procedure that varies in stimulation type, acupoint selection, needling depth, manipulation technique, etc. Manipulation techniques are quite different across various regions of the world, and IPD may help to explore the predictors of the outcome, which may help to improve the efficacy of acupuncture.

To date, most IPD meta-analyses have used a two-stage approach [49]. Although the one-stage and two-stage approaches usually yield similar estimates of treatment effects [50], one-stage models are preferable in some situations, and their use has increased dramatically in recent years [51]. A one-stage approach can allow for differences between studies by including study-specific effects in the statistical model [52]. We are still interested in investigating the interaction between patient characteristics and treatment effects, and a one-stage model is preferred in this situation [53].

Patient-level data are often difficult to obtain from researchers. We are taking two measures to obtain IPD. One of our IPD sources is the CACMS CliniRsearch Data Management System. In addition, we plan to contact authors through two acupuncture associations, namely, the China Association of Acupuncture-Moxibustion and the World Federation of Acupuncture-Moxibustion Societies, as we are in close contact with the secretariats of these two associations. Through these two acupuncture associations, of which one is the largest such group based in China and the other is the largest in the world, we can gain access to acupuncture researchers and gain trust from them.

Finally, this review will provide IPD-based meta-analysis evidence regarding the effects of acupuncture on constipation, and it will explore the factors predicting these effects, which may help to improve the

management of constipation.

Abbreviations

AGA - American Gastroenterological Association

AMED- Allied and Alternative Medicine

APD- aggregate patient data

CACMS- China Academy of Chinese Medical Sciences

CBMdisc- China Biology Medicine disc

CBSM- complete spontaneous bowel movements

CENTRAL- Cochrane Central Register of Controlled Trials

CNKI -China National Knowledge Infrastructure

ESNM- European Society of Neurogastroenterology and Motility

GRADE - Grading of Recommendations Assessment, Development and Evaluation

ICTRP - International Clinical Trials Registry Platform

IPD- individual patient data

ITT- intention-to-treat

LOCF- last observation carried forward

PAC-QOL- Patient Assessment of Constipation Quality of Life questionnaire

RCT- randomized controlled trials

RoB -Risk of Bias

SBM -spontaneous bowel movement

Declarations

Ethics approval and consent to participate

Ethical approval is not required for a systematic review and meta-analysis. IPD data would be de-identified, and statistical analysis would be used for research purposes only.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YA is the guarantor. CC drafted the manuscript. All authors contributed to the development of the selection criteria and data extraction criteria. CC developed the search strategy. YA and XL designed the statistical analysis methods. NG provided expertise on functional constipation. All authors read the manuscript, provided feedback and approved the final version.

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