

INPLASY PROTOCOL

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Review Stage at time of this submission: The review has not yet started.

Conflicts of interest:
None declared.

INTRODUCTION

Review question / Objective: Is acupuncture a safe and effective therapy for constipation associated with

The effectiveness and safety of acupuncture for constipation associated with Parkinson's disease: Protocol for a systematic review and meta-analysis

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Review question / Objective: Is acupuncture a safe and effective therapy for constipation associated with Parkinson's disease? Our aim is to assess the effectiveness and safety of acupuncture for constipation associated with PD and give guidance to future research direction.

Condition being studied: Parkinson's disease (PD) is a prevalent degenerative disease of nervous system characterized mainly by static tremor, bradykinesia, myotonia, postural gait disorders and other non-motor symptoms. According to variations on race, ethnicity, age and sex, the incidence of PD ranges from 8 to 20.5 per 100, 000 individuals annually. One global research shows that there were 6.1 million individuals suffer from PD in 2016 and will be 12 million patients around the world. According to several outcomes of case-control studies, the prevalence of constipation in PD varies from 28% to 61%. Constipation, as a common gastrointestinal disease which refers to the clinical presentation of reduced spontaneous complete bowel movement, dyschezia, feeling of incomplete defecation and outlet obstruction, is demonstrated to antedate the motor symptom and it's severity is related to the progression of PD. Acupuncture has been proved to act on the pathogenesis of constipation associated with PD. The proposed systematic review we're about to present is the first advanced evidence-based medical evidence in this area.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 February 2022 and was last updated on 22 February 2022 (registration number INPLASY202220091).

Parkinson's disease? Our aim is to assess the effectiveness and safety of acupuncture for constipation associated with PD and give guidance to future research direction.

Rationale: Parkinson's disease (PD), a prevalent degenerative disease of nervous system characterized mainly by static tremor, bradykinesia, myotonia, postural gait disorders and other non-motor symptoms. According to variations on race, ethnicity, age and sex, the incidence of PD ranges from 8 to 20.5 per 100,000 individuals. According to several outcomes of case-control studies, the prevalence of constipation in PD varies from 28% to 61%. Constipation is demonstrated to antedate the motor symptom and its severity is related to the progression of PD. Excessive distention of the intestinal wall caused by constipation may render delay or failure of medication absorption. Otherwise, constipation is also an important predisposing factor of emergency admissions for complications of PD like intestinal obstruction, perforation and pulmonary aspiration. Hence management of constipation is important in the treatment and progression of Parkinson's disease. Currently, symptomatic treatment is the main therapy for PD with constipation including osmotic laxatives, irritant laxatives and chloride channel activators. Psyllium, as an osmotic laxative, is proved to have a positive effect on the frequency of bowel movements in patients with PD, but it also requires sufficient water intake, or it may exacerbate constipation. Polyethylene glycol is an osmotic laxative which is recommended by the American Academy of Neurology and the International Parkinson and Movement Disorder Society Evidence-Based Medicine Committee. A randomized double-blind trial shows that polyethylene glycol can obviously improve the frequency of bowel movements ($P < 0.002$) and fecal consistency ($P < 0.006$) without affecting motor symptoms of PD. However, osmotic laxatives can cause electrolyte disturbance and hypervolemia, so they should be used with caution in elderly patients to prevent renal and cardiac dysfunction. Lubiprostone, a chloride channel activator, is approved by the US FDA to treat chronic idiopathic constipation and irritable bowel syndrome with constipation. A double-blind, placebo controlled, randomized clinical trial suggests that by contrast to

placebo Lubiprostone can improve patients' constipation rating scale ($p < 0.05$), visual analog scale ($p = 0.001$) and number of bowel movements per day ($p < 0.001$). Adverse reactions include intermittent diarrhea, nausea, vomit. All these drugs mentioned above have been shown to improve constipation on PD, but they all have side effects more or less. Most importantly, they can't affect the pathogenesis of constipation. Alpha-synuclein (Lewy bodies) plays an important role in the pathogenesis of PD. Pathological research finds that α -synuclein accumulate in enteric nervous system (ENS) in early PD. Furthermore, the expression of α -synuclein in intestine was higher in patients with PD than in control group, and α -synuclein inclusion bodies were present in the gastrointestinal tract of patients at all stages of PD. Another research shows that α -synuclein has a positive correlation with PD Rating Scale score and the severity of constipation. Therefore, the accumulation of α -synuclein in ENS may cause the onset of constipation. Recent research finds that acupuncture and electroacupuncture can down-regulate the expression of α -synuclein in mice colon and relieve the symptoms of PD. Acupuncture is a unique complementary and alternative therapy. It works by inserting needles in certain acupoints and then lifting, thrusting, twirling needles manually or electrically to acquire the De Qi sensation — sensations of sourness, numbness, heaviness and distension. Acupuncture has been accepted by many countries around the world. Recently, some clinical researches show that acupuncture has a positive effect on constipation in PD. The proposed systematic review we're about to present is the first advanced evidence-based medical evidence in this area. Our aim is to assess the effectiveness and safety of acupuncture for constipation associated with PD and give guidance to future research direction.

Condition being studied: Parkinson's disease (PD) is a prevalent degenerative disease of nervous system characterized mainly by static tremor, bradykinesia,

myotonia, postural gait disorders and other non-motor symptoms. According to variations on race, ethnicity, age and sex, the incidence of PD ranges from 8 to 20.5 per 100, 000 individuals annually. One global research shows that there were 6.1 million individuals suffer from PD in 2016 and will be 12 million patients around the world. According to several outcomes of case-control studies, the prevalence of constipation in PD varies from 28% to 61%. Constipation, as a common gastrointestinal disease which refers to the clinical presentation of reduced spontaneous complete bowel movement, dyschezia, feeling of incomplete defecation and outlet obstruction, is demonstrated to antedate the motor symptom and it's severity is related to the progression of PD. Acupuncture has been proved to act on the pathogenesis of constipation associated with PD. The proposed systematic review we're about to present is the first advanced evidence-based medical evidence in this area.

METHODS

Search strategy: The search methods in this study include electronic search and manual search. The selected databases are consisted of PubMed, Embase, Springer, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure, the China Biomedical Literature Database, the Chinese Scientific Journal Database and the Wan-Fang Database. All the articles from inception to March 2022 will be retrieved. The following search terms are mainly extracted from MeSH Database: constipation, dyschezia, Parkinson Disease, idiopathic Parkinson's Disease, Parkinson's Disease, Lewy Body Parkinson's Disease, idiopathic Parkinson Disease, Lewy Body Parkinson Disease, primary Parkinsonism, paralysis agitans, acupuncture, acupuncture therapy, electroacupuncture, abdominal acupuncture, ear acupuncture, auricular acupuncture, warm acupuncture, fire needling, press-needle. The same terms will be searched in Chinese databases after translating. We will search articles in three

electronic database including PubMed, Embase, Springer, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure, the China Biomedical Literature Database, the Chinese Scientific Journal Database and the Wan-Fang Database. All the published randomized controlled trials(RCTs) that assessed acupuncture therapy for constipation associated with PD from the inception date of each database up to 1 March 2022 will be included. We will exclude crossover trials, self-controlled trials, case report, and fundamental experiment study to avoid the onset of bias. In view of language limitation of researchers, only Chinese and English literatures will be included.

Participant or population: Since constipation is a complication of PD, the participants should meet both the Movement Disorder Society(MDS) clinical diagnostic criteria for PD published in 2015 or other diagnostic criterias for PD and Rome III/IV diagnostic criteria for constipation. No limitations on age, race, gender and ethnicity.

Intervention: Manual acupuncture, abdominal acupuncture, electro-acupuncture, warm acupuncture, fire needling, press-needle and ear acupuncture will be included. Acupuncture associated with other positive therapy will also be considered. There are no limitations on needle materials, needling manipulation, stimulus intensity and frequency. Those therapies without needle insertion such as massage, moxibustion will beyond consideration.

Comparator: Traditional Chinese medical herbal treatment(oral/external), western medicine therapy, massage, diet therapy, sham acupuncture, conventional therapy and psychological intervention will be included. One point to note is that comparators or control groups involve other kinds of acupuncture or identical acupuncture therapy with different acupoints or manipulation shoule be excluded.

Study designs to be included: All the published randomized controlled trials(RCTs) that assessed acupuncture therapy for constipation associated with PD from the inception date of each database up to 1 March 2022 will be included. We will exclude crossover trials, self-controlled trials, case report, and fundamental experiment study to avoid the onset of bias. In view of language limitation of researchers, only Chinese and English literatures will be included.

Eligibility criteria: 1.Types of studies: All the published randomized controlled trials(RCTs) that assessed acupuncture therapy for constipation associated with PD from the inception date of each database up to 1 March 2022 will be included. We will exclude crossover trials, self-controlled trials, case report, and fundamental experiment study to avoid the onset of bias. In view of language limitation of researchers, only Chinese and English literatures will be included. 2.Types of participants: Since constipation is a complication of PD, the participants should meet both the Movement Disorder Society(MDS) clinical diagnostic criteria for PD published in 2015 37 or other diagnostic criterias for PD and Rome III/IV diagnostic criteria for constipation38-39. No limitations on age, race, gender and ethnicity. 3. Types of interventions: Manual acupuncture, abdominal acupuncture, electroacupuncture, warm acupuncture, fire needling, press-needle and ear acupuncture will be included. Acupuncture associated with other positive therapy will also be considered. There are no limitations on needle materials, needling manipulation, stimulus intensity and frequency. Those therapies without needle insertion such as massage, moxibustion will beyond consideration.4. Types of comparator(s)/control: Traditional Chinese medical herbal treatment(oral/external), western medicine therapy, massage, diet therapy, sham acupuncture, conventional therapy and psychological intervention will be included. One point to note is that comparators or control groups involve other kinds of acupuncture or

identical acupuncture therapy with different acupoints or manipulation should be excluded.

Information sources: The search methods in this study include electronic search and manual search. The selected databases are consisted of PubMed, Embase, Springer, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure, the China Biomedical Literature Database, the Chinese Scientific Journal Database and the Wan-Fang Database. All the articles from inception to March 2022 will be retrieved. Searching other resources To ensure the integrity of the included studies, we will take other ways to make up for possible omissions. With regard to ongoing RCTs, we will further search the WHO International Clinical Trials Registry Platform(<http://www.who.int/trialsearch>), metaRegister of Controlled Trials(<http://www.controlledtrials.com>), United States National Institutes of Health Ongoing Trials Register(<http://www.clinicaltrials.gov>), and the Chinese Clinical Trial Registry(<http://www.chictr.org/cn/>). We will contact the corresponding author to get the latest clinical data. Other references in related review or systematic review will be inspected attentively to identify additional trials. Conference articles or some medical journals will be manual searched in university and national library.

Main outcome(s): The primary outcomes of this review will be the change of mean frequency of spontaneous bowel movements(SBMs) and variation on the Bristol Stool Form Scale score.

Additional outcome(s): The secondary outcomes include traditional Chinese medicine(TCM) clinical efficacy score, score of constipation patients quality of life scale(PAC-QOL), Cleveland constipation score(CSS), score of Unified Parkinson's Disease Rating Scale (UPDRS) and safety assessment. TCM clinical efficacy score should be conducted according to diagnostic and therapeutic criteria of TCM diseases or other criteria specially designed for TCM. We will evaluate the safety of the treatment by analysing the

incidence of adverse reactions(AEs) include fainting, local bleeding, ecchymosis, flatulence, abdominal pain and diarrhoea et al.

Quality assessment / Risk of bias analysis:

Two reviewers are arranged to evaluate the risk of bias of eligible studies by using the Cochrane Collaboration's bias risk assessment tool. Seven evaluation contents are listed as follow: random sequence generation, allocation concealment, blinding of subjects and implementers, blinding of estimators and statisticians, incomplete result data, selective reporting of research results and other deviation sources. Each content will be divided into three levels(low, high, unclear). If a conflicting result appears, the third reviewer will be invited to give a final decision. As long as unclear information show up, we will contact with corresponding author timely.

Strategy of data synthesis: RevMan 5.4 software will be used to conduct statistical analysis. As for the dichotomous variable, the risk ratio(RR) with 95% confidence intervals(CIs) will be used. For continuous result data, the standard mean difference(SMD) or weighted mean difference will be used. Analysis of heterogeneity in this review is implemented according to Cochrane Handbook⁴². χ^2 test serves as a method to assess the heterogeneity. If $p < 0.1$, the result will be deemed statistically significant. Additionally, we will use I² index to evaluate the statistical inconsistency of the eligible studies. When $p \leq 50\%$, the random-effects model will be used. The fixed-effects model will be utilized when $p \geq 0.1$ and $I^2 \leq 50\%$. To explore the reason of heterogeneity, subgroup analysis or meta-regression will be performed.

Subgroup analysis: Subgroup analysis is a way to investigate the causes of heterogeneity or inconsistency. In this review, the subgroup analysis will be conducted in accordance with the heterogeneity of age, sex, acupuncture type(main factor), manipulation of acupuncture, intervention of control group,

the severity of constipation and other disparate control interventions.

Sensitivity analysis: Sensitivity analysis is a methodology to reanalysis the review conclusion in order to ensure the robustness of the review. In this review, sensitivity analysis will be laid out on the basis of sample size, heterogeneity quality and statistical model.

Language: In view of language limitation of researchers, only Chinese and English literatures will be included.

Country(ies) involved: China.

Keywords: Acupuncture; Parkinson's Disease; Constipation; Protocol; Systematic review.

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