INPLASY PROTOCOL

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Corresponding author:
Zhijie Li

tcm_1234@163.com

Author Affiliation:
Hubei University of Chinese Medicine; Wuhan Hospital of Traditional Chinese Medicine; Hunan University of Chinese Medicine.

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Conflicts of interest:
None declared.

Chinese Medicine Therapies for Neurogenic Bladder after Spinal Cord Injury: A protocol for systematic review and network meta-analysis

Zhu, ZH[1]; Zhuo, Y[2]; Jin, HT[3]; Wu, BY[4]; Li, ZJ[5].

Review question / Objective: **Neurogenic bladder (NB), a refractory disease, is characterized by voiding dysfunction of bladder and/or urethra, and spinal cord injury (SCI) is a common cause. Chinese medicine therapies have been applied extensively in the treatment of neurogenic bladder, especially in China, and the results are promising but varying. Thus, the aim of this work is to assess the efficacy and safety of various Chinese medicine therapies for neurogenic bladder after spinal cord injury.**
Condition being studied: **Chinese medicine therapies; Neurogenic bladder after spinal cord injury.**
Main outcome(s): **The primary outcome of our NMA will be measured by overall response rate and urodynamic tests, which includes postvoiding residual urine volume, maximum urinary flow rate, and maximal detrusor pressure.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 August 2021 and was last updated on 21 August 2021 (registration number INPLASY202180084).

INTRODUCTION

Review question / Objective: **Neurogenic bladder (NB), a refractory disease, is characterized by voiding dysfunction of bladder and/or urethra, and spinal cord injury (SCI) is a common cause. Chinese medicine therapies have been applied extensively in the treatment of neurogenic bladder, especially in China, and the results are promising but varying. Thus, the aim of this work is to assess the efficacy and**

safety of various Chinese medicine therapies for neurogenic bladder after spinal cord injury.

Condition being studied: Chinese medicine therapies; Neurogenic bladder after spinal cord injury.

METHODS

Participant or population: The patients who are diagnosed with NB after SCI by a clear and widely recognized criterion will be recruited, and irrespective of gender, age, nationality, race.

Intervention: For the experimental groups, Chinese medicine interventions or their combinations, based on the classification criteria of State Administration of Chinese medicine of China, must be applied in the experimental groups and regardless of differences in the specific prescription, duration, or frequency of treatments. In order to align with clinical practice and increase generalizability of our findings, we will merge similar therapies into 10 types of interventions (Acupuncture therapy, Electroacupuncture therapy, Acupoint sticking therapy, Acupoint injection therapy, Moxibustion therapy, Tuina/ Massage therapy, Oral Chinese herb medicine, Herb fumigation/soaking therapy, Scrapping therapy, Cupping therapy).

Comparator: The control groups with non-Chinese medicine interventions, consisting of non- surgical conservative therapies (intermittent catheterization, indwelling catheters, pelvic-floor electro-stimulation, bladder training, medications, and so on) and blank control methods (placebo, sham acupuncture, and so on), will be included in our NMA.

Study designs to be included: All randomized controlled trials (RCTs) of testing Chinese medicine therapies for NB after SCI will be eligible for our study without any limitation of population characteristics. However, the language is limited to English or Chinese, and non-RCTs such as meeting abstracts, clinical experience, system reviews, case reports, and animal trials will be removed. Apart from this, sufficiency of original data is indispensable.

Eligibility criteria: (1) Types of studies: All randomized controlled trials (RCTs) of testing Chinese medicine therapies for NB after SCI will be eligible for our study without any limitation of population characteristics. However, the language is limited to English or Chinese, and non-RCTs such as meeting abstracts, clinical experience, system reviews, case reports, and animal trials will be removed. Apart from this, sufficiency of original data is indispensable. (2) Types of participants: The patients who are diagnosed with NB after SCI by a clear and widely recognized criterion will be recruited, and irrespective of gender, age, nationality, race. (3) Types of interventions: In the experimental groups, Chinese medicine interventions or their combinations, based on the classification criteria of State Administration of Chinese medicine of China, must be applied and regardless of differences in the specific prescription, duration, or frequency of treatments. In order to align with clinical practice and increase generalizability of our findings, we will merge similar therapies into 10 types of interventions (Acupuncture therapy, Electroacupuncture therapy, Acupoint sticking therapy, Acupoint injection therapy, Moxibustion therapy, Tuina/ Massage therapy, Oral Chinese herb medicine, Herb fumigation/soaking therapy, Scrapping therapy, Cupping therapy), and the control groups with non-Chinese medicine interventions, consisting of non-surgical conservative therapies (intermittent catheterization, indwelling catheters, pelvic-floor electro-stimulation, bladder training, medications, and so on) and blank control methods (placebo, sham acupuncture, and so on), will be included in our NMA. (4) Types of outcomes: The primary outcome of our NMA will be measured by overall response rate and urodynamic tests, which includes postvoiding residual urine volume, maximum urinary flow rate, and maximal detrusor pressure. The secondary outcome includes a voiding diary (the number of

patients with retention or incontinence, their average number of urination or incontinence episodes per 24 hours), clinical assessments (e.g., 1h/24h pad test), QoL questionnaire. Apart from this, safety assessments, for instance, drop-out cases and adverse events will be considered as well.

Information sources: A comprehensive search for potentially relevant literature will be performed in 8 online databases from their establishment throughout June 2021: the Cochrane Library, Web of Science, PubMed, EMBASE Database, China Biological Medicine Database (CBM), Chinese Scientific Journals Database (VIP), Wan Fang databases and China National Knowledge Infrastructure (CNKI). Search strategy based on MeSH terms combining with free text words will be applied in English databases, while counterpart terms in Chinese will be used in Chinese databases. Additionally, the related references of included literature will also be screened carefully under the guidance of the snowball strategy, and the language will be limited to English or Chinese. If the information we need is incomplete, we will contact the corresponding author to obtain it, and an intention-to-treat (ITT) analysis will also be conducted for missing or unreachable data.

Main outcome(s): The primary outcome of our NMA will be measured by overall response rate and urodynamic tests, which includes postvoiding residual urine volume, maximum urinary flow rate, and maximal detrusor pressure.

Additional outcome(s): The secondary outcome includes a voiding diary (the number of patients with retention or incontinence, their average number of urination or incontinence episodes per 24 hours), clinical assessments (e.g., 1h/24h pad test), QoL questionnaire. Apart from this, safety assessments, for instance, drop-out cases and adverse events will be considered as well.

Data management: The first step is to import the retrieved literature into EndNote X8 to remove duplicates automatically, then primary screening will be performed independently by two reviewers based on titles and abstracts, and studies not meeting the selection criteria will be removed directly. The second step is to conduct a full-text screening to select eligible articles by the same two reviewers, and the exclusion reasons will be recorded individually. The third step is to carry out a cross-checked of the results to ensure the consistency of the screening. When the disagreements appeared, a third senior assessor will be asked to assist in the ultimate judgement. When the above steps are completed, a data extraction table, which mainly includes first author's name, nationality, publication year, participants' characteristics (sample size, gender, mean age, number of groups, type of NB after SCI, disease duration, 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 well-trained researchers will independently assess the bias risk of all the included RCTs by the Cochrane Collaboration tool, which consisted of the following aspects: assignment concealment, random sequence generation, blinding of outcome assessors, blinding of participants and personnel, selective reporting, the integrity of outcome data, and other sources of bias. Each field has been classified as high risk, low risk, or unclear risk. Any disagreements will be resolved by discussion with a third senior assessor.

Strategy of data synthesis: First of all, a pairwise meta-analysis will be performed using Revman 5.3. (Cochrane Collaboration, Oxford, UK) for the direct comparisons. Secondly, considering the anticipated heterogeneity, the NMA within a Bayesian framework will be conducted by WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) based on the random effect model for the results of the indirect comparison. Besides, 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. Additionally, 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 computed by STATA 14.0. (Stata Corporation, College Station, Texas, USA) to forecast the possible ranking order. In our study, a higher SUCRA score represents the better Chinese medicine intervention for NB after SCI.

Subgroup analysis: In case significant heterogeneity is identified, subgroup analysis will be performed according to the possible sources of heterogeneity, such as type of NB after SCI (retention or incontinence), injured spinal segments, quality of studies.

Sensitivity analysis: Considering that varying level of the methodological quality of trails may tend to affect our findings, sensitivity analysis will be performed to evaluate the robustness of the results by excluding high-risk studies.

Language: The language is limited to English or Chinese.

Country(ies) involved: China.

Keywords: traditional Chinese medicine, neurogenic bladder, spinal cord injuries, network meta-analysis, systematic review, protocol.

Contributions of each author:

Author 1 - Zhihong Zhu - Conceptualization; Data curation; Data analysis; Manuscript writing.
Email: 467548583@qq.com
Author 2 - Yue Zhuo - Methodology; Data analysis.
Email: nedved823@qq.com
Author 3 - Haitao Jin - Data curation.
Author 4 - Boyu Wu - Methodology; Data analysis.
Author 5 - Zhijie Li - Conceptualization; Supervision.