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Acupuncture for neurogenic bladder due to spinal cord injury: a systematic review protocol

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ABSTRACT

Introduction: Neurogenic bladder is one of the most common complications following spinal cord injury (SCI). In China, acupuncture therapy is a common treatment for neurogenic bladder due to SCI, but its effects and safety remain uncertain. A protocol is described for a systematic review to investigate the beneficial effects and safety of acupuncture for neurogenic bladder due to SCI.

Methods and analysis: Eight databases will be searched from their inception: the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the China National Knowledge Infrastructure (CNKI), the VIP database, the Wanfang database, the China Doctoral Dissertations Full-text Database (CDFD) and the China Master's Theses Full-text Database (CMFD). Any clinical randomised controlled trials (RCTs) and the first period of randomised cross-over studies related to acupuncture for neurogenic bladder due to SCI will be included. Outcomes will include change in urinary symptoms, urodynamic tests, clinical assessment and quality of life (QoL). The incidence of adverse events will be assessed as the safety outcome. Study selection, data extraction and quality assessment will be performed independently by two reviewers. Assessment of risk of bias, data synthesis and subgroup analysis will be carried out using Review Manager software.

Ethics and dissemination: Ethics approval is not required as this is a protocol for a systematic review. The findings of this systematic review will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: PROSPERO (CRD42014010448).

Strengths and limitations of this study

- Study selection, data extraction and quality assessment will be performed by two reviewers independently.
- The authenticity of the included studies will be corroborated by searching relevant published protocols and contacting the first or corresponding author.
- The variety of acupuncture therapies used may make data synthesis and subgroup analysis more difficult.
- Because of the language barrier, Korean and Japanese medical databases will not be covered and some related studies might be missed.

INTRODUCTION

Description of the condition

Neurogenic bladder due to spinal cord injury (SCI) refers to bladder dysfunction caused by damage to bladder neural circuits following SCI. It is characterised by lower urinary tract symptoms and is usually followed by complications.[1] The clinical manifestations of neurogenic bladder dysfunction (NBD) include urinary incontinence and urine retention. The underlying pathological mechanisms of NBD symptoms are detrusor overactivity and detrusor-sphincter dyssynergia, depending on the damaged segment of spinal cord and the duration of disease.[2 3]

Studies have indicated that the incidence of neurogenic bladder is approximately 69–92% among SCI patients,[4–7] with annual morbidity varying from 14 to 53 per million population.[8 9] It is believed that neurogenic bladder is a major problem, is associated with poor prognosis and is one of the most common complications in SCI patients.[4 10 11] In addition, long-term rehabilitation imposes a heavy economic burden. The US government spends nearly US$16.3 billion each year to treat neurogenic bladder.[12] Therefore, continuous and effective low-cost treatment is needed to improve urinary symptoms and reduce medical costs.

Description of the intervention

Acupuncture, which has been used for more than 2500 years to cure disease and relieve pain, plays an important role in Traditional Chinese Medicine (TCM).[13] It is a minimally invasive procedure in which thin metal needles are inserted into specific body points

and either slowly twisted manually or stimulated electrically. Acupuncture therapy is popular among Chinese people due to its simple operation, low cost and few adverse effects. It is also increasingly practiced and requested by patients and their family members in some western countries.[14] In 1979, the WHO drew up a provisional list of 47 diseases that could potentially be treated with acupuncture, including neurogenic bladder due to SCI.[15 16]

How the intervention might work

Studies have indicated that acupuncture might affect the synthesis and release of neurotransmitters which regulate the physiological function of the bladder, such as substance P, nitric oxide synthase and calcitonin gene-related peptide.[17–19] In addition, acupuncture could affect discharge frequency controlled by the micturition centres in the central nervous system.[20] Furthermore, acupuncture could promote the GABAergic system and hinder activation of C-fibres by bladder sensory afferent fibres if needles are inserted at the points near the posterior sacral foramina.[21–25] In the last 2 years, researchers have begun to focus on the neurorehabilitation and neuroplasticity effects of electroacupuncture for neurogenic bladder due to SCI.[26 27]

Why it is important to do this review

Currently, acupuncture therapy is a common treatment for neurogenic bladder due to SCI in China. In addition, the number of published intervention studies on the use of acupuncture for this condition has grown markedly over the last few years. Although a systematic review of acupuncture for neurogenic bladder after SCI was published in 2013, the result of the review was inconclusive due to the serious methodological defects of the included studies and the small number of trials assessed in meta-analyses.[28] It remains uncertain whether acupuncture is effective and safe. Clinical evidence needs to be identified, appraised, graded and summarised for the benefit of both patients and clinicians.

OBJECTIVES

The objective of this systematic review is to determine whether acupuncture is effective and safe in relieving urinary symptoms, and whether it produces better results in urodynamic tests and improves quality of life (QoL) in patients with neurogenic bladder due to SCI. When possible, both the short-term and the long-term effects will be evaluated.

METHODS

The methods for this systematic review have been developed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[29]

Criteria for considering studies for this review

Types of studies

All clinical randomised controlled trials (RCTs) and the first period in randomised cross-over trials will be included in the review, regardless of publication status. Trials will be excluded if they are non-randomised controlled trials, non-randomised cross-over trials, retrospective studies, before-and-after studies or studies that are purely research studies into the mechanisms of acupuncture.

Types of participants

All participants of any age or gender with stable vital signs, diagnosed with neurogenic bladder caused by SCI, will be included, irrespective of date of injury, its level or its severity. Individuals with neurogenic bladder caused by other diseases such as diabetes mellitus, stroke, tumour, dementia, multiple system atrophy, Parkinson's disease, multiple sclerosis, Guillain-Barre syndrome, spinal canal stenosis, lumbar disc disease or syringomyelia will be excluded. Participants who have undergone a surgical operation for neurogenic bladder will also be excluded.

Types of interventions

Interventions in the treatment group will include any kind of acupuncture regardless of the site or type of treatment, such as whole body acupuncture, scalp acupuncture, auricular acupuncture, electroacupuncture, fire needling, warm needling, elongated needling, intradermal needling, etc. Acupuncture combined with other conservative treatments will also be included. The control intervention can include no active treatment, sham acupuncture, medication/drugs, rehabilitation (such as bladder training, pelvic-floor muscle exercises, pelvic-floor electro-stimulation and biofeedback), external appliances (condom catheters, pads or penile clamps) or other conservative treatments such as catheterisation (intermittent or indwelling). However, combined interventions consisting of four or more therapies or with potential safety problems will be excluded.

Types of outcome measures

The primary outcome is the difference in urinary symptoms before and after treatment, as reported by participants in a voiding diary or a self-report questionnaire. It includes the mean number of urination and/or incontinence episodes per 24 h, the number of participants with incontinence or retention, and the number of participants requiring catheterisation.

The secondary outcomes include the following items: (1) changes in urodynamic tests before and after treatment, for example, maximum urinary flow rate (Qmax), postvoiding residual urine volume (RUV) and maximal detrusor pressure; (2) change in clinical assessment before and after treatment, for example, the standardised pad test (1 h or 24 h; quantified leakage), severity of incontinence, and incidence of recurrent urinary

incontinence or retention; (3) change in a QoL questionnaire before and after treatment, for example, condition-specific QoL measures, general health QoL measures and psychologically related scales; and (4) the effective rate.

Safety outcome measures include the incidence of all reported adverse events such as local pain, haematomas, fainting during acupuncture treatment, and complications related to neurogenic bladder.

Search methods for identification of studies

Electronic searches

The following databases will be searched from their inception, irrespective of publication status: the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the China National Knowledge Infrastructure (CNKI), the VIP database, the Wanfang database, the China Doctoral Dissertations Full-text Database (CDFD) and the China Master's Theses Full-text Database (CMFD).

Studies will also be obtained from the following sources: the reference lists of all included studies or relevant reports of clinical trials or review articles; unpublished conference proceedings relevant to neurogenic bladder due to SCI; and ongoing trials which will be searched through the WHO international clinical trials registry platform (http://apps.who.int/trialsearch/) and Current Controlled Trials (http://www.controlled-trials.com).

Search strategy

The search will be conducted in English and Chinese using the following terms:

A. Search strategy to locate 'spinal cord injury':
- # 1 spinal cord injury
- # 2 spinal cord trauma
- # 3 spinal cord contusion
- # 4 spinal cord lesion
- # 5 paraplegia
- # 6 or/1-5

B. Search strategy to locate 'neurogenic bladder':
- # 7 neurogenic bladder
- # 8 bladder disorder
- # 9 uninhibited bladder
- # 10 bladder dysfunction
- # 11 emiction disorder
- # 12 aconuresis
- # 13 incontinence
- # 14 retention
- # 15 uroschesis
- # 16 or/7–15

C. Search strategy to locate acupuncture interventions:
- # 17 acupuncture
- # 18 electroacupuncture
- # 19 fire needle
- # 20 body acupuncture
- # 21 warm needle
- # 22 auricular acupuncture
- # 23 scalp acupuncture
- # 24 elongated needle
- # 25 intradermal needle
- # 26 or/17–25
- # 27 6 and 16 and 26

Data collection and analysis

Selection of studies

Clinical studies will be identified and included by two independent reviewers (TZ and HL) according to the inclusion criteria. The two reviewers will read the titles, abstracts and full texts if necessary, and collect the studies meeting the inclusion criteria. The authenticity of the collected studies will be checked directly by searching related published protocols and contacting the first or corresponding author. If telephone numbers are not available, email or post will be used. Suitable RCTs will be selected and cross-checked by the two reviewers (TZ and HL). Any disagreement will be discussed after cross-checking and adjudicated by the third reviewer (LW). The process of studies selection is presented in a PRISMA flow diagram (figure 1).

Data extraction and management

Two independent researchers (TZ and HL) will extract the data from the included studies into an extraction form developed according to recommendations in the Cochrane Handbook. The extraction form consists of 10 major items: general information (author, working location, publication date, journal, etc), the participants, characteristics of interventions, outcomes, randomisation, allocation concealment, incomplete data, blinding, selective report, and conflicts of interest. The result of data extraction will also be cross-checked. Any disagreement will be discussed and adjudicated by a third reviewer (LW).

Assessment of risk of bias in included studies

The risk of bias will be evaluated by two reviewers independently. The result of the assessment will also be cross-checked. Any disagreement will be discussed and adjudicated by a third reviewer. According to the methods for assessing risk of bias using the 'Risk of bias' tool of the Cochrane Handbook (V.5.1.0), the studies will be categorised as 'high risk' of bias, 'low risk' of bias, or 'unclear risk' of bias. The following types of bias will be assessed: (1) selection bias: random sequence generation and allocation concealment; (2) performance bias: blinding of investigators, participants and care providers; (3) detection bias: blinding of outcome assessment; (4) attrition bias: incomplete data/differential dropout; (5) reporting bias: selective reporting; (6) other bias: for example, conflict of interest, follow-up, non-intention-to-treat or per-protocol analysis, etc.

Measures of treatment effect

For dichotomous data, the results of each study will be pooled and presented as a risk ratio with 95% CIs. A

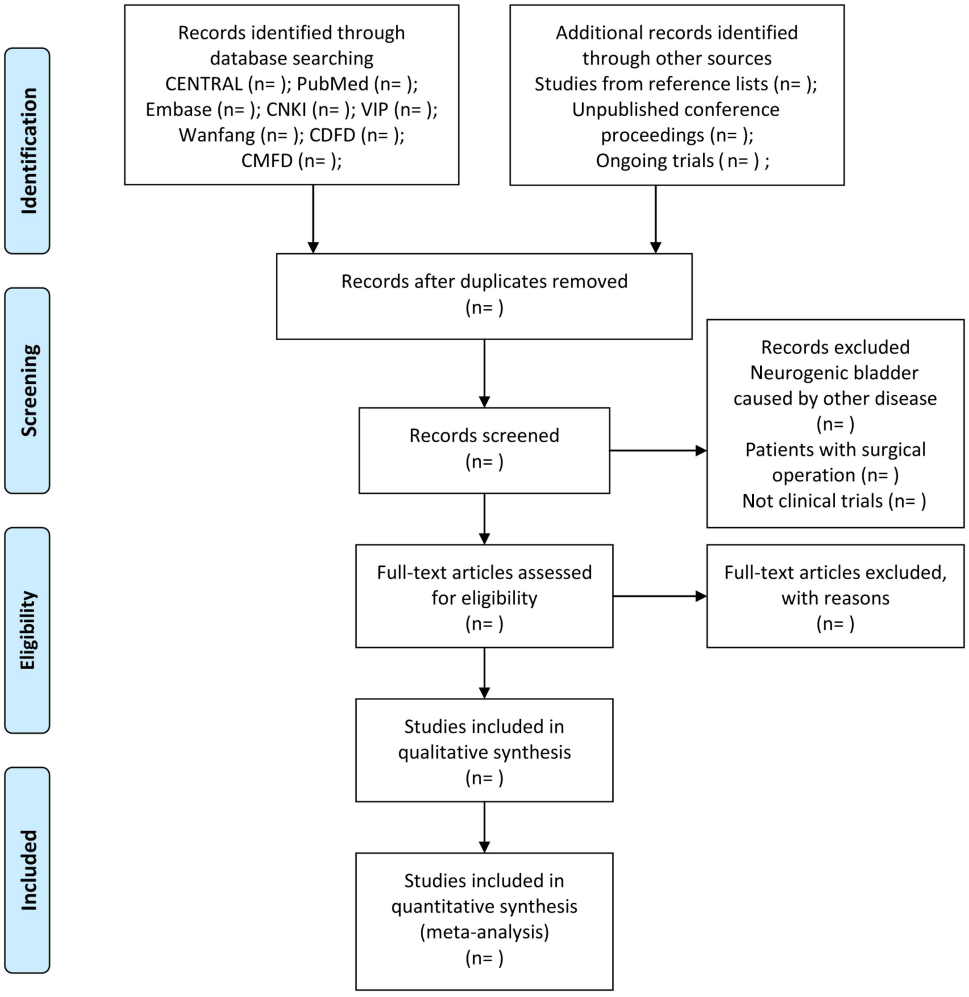

Figure 1 Flow diagram of the trial selection process.

mean difference with 95% CI will be used for continuous data.

Dealing with missing data

If required data are ambiguous or not reported in the clinical articles, reviewers will contact the first or corresponding author of the studies by telephone, email or post and collect the missing data using the data extraction form.

Assessment of heterogeneity

The heterogeneity of the studies will be assessed before meta-analysis based on clinical similarities in populations and interventions. Clinical and methodological heterogeneity will be judged according to the data recorded on the extraction form. Statistical heterogeneity will be calculated by using the Mantel-Haenszel χ^2 test for heterogeneity. A result with a p value <0.10 and a high I^2 value indicates statistically significant heterogeneity. According to the Cochrane Handbook, I^2 values can be classified into four categories: a value of 0–40% indicates little or no heterogeneity; a value of 30–60% indicates moderate heterogeneity; a value of 50–90% indicates substantial heterogeneity; and a value of 75–100% indicates considerable heterogeneity. Statistical heterogeneity also depends on the magnitude of effects, the direction of results and the strength of evidence.

Assessment of reporting biases

Reviewers will search for the published protocols of the trials or contact the first or corresponding author of the study to acquire information regarding selective reporting. The result will be judged as having a 'high risk' of bias, a 'low risk' of bias or an 'unclear risk' of bias according to the criteria of the 'Risk of bias' assessment tool of the Cochrane Handbook (V.5.1.0). Funnel plots will be generated to analyse the potential publication bias if more than 10 trials are included.

Data synthesis

Data synthesis will be carried out using Review Manager (V.5.2) statistical software provided by the Cochrane Collaboration. If two or more eligible studies with low clinical, methodological and statistical heterogeneity are identified, the studies will be combined for meta-analysis. We will consider using the random-effects

model during the meta-analysis. For the cross-over studies, only data from the period before the first cross-over will be analysed.

Subgroup analysis

If a sufficient number of randomised trials are identified, subgroup analyses will be performed according to: (1) different types of acupuncture therapy; (2) neurological level of SCI (low vs high); (3) treatment duration (eg, less than or more than 2 weeks); and (4) clinical manifestation of neurogenic bladder (incontinence or retention).

Sensitivity analysis

Sensitivity analysis will be carried out when significant heterogeneity still exists after subgroup analysis and when no errors are found in the data input steps. The meta-analysis will be repeated after lower quality studies are excluded. The results of these two meta-analyses will then be compared. It will be decided by discussion whether the lower quality studies will be excluded or not, depending on their sample size, strength of evidence and influence on the pooled effect size.

DISCUSSION

This systematic review will provide the latest analysis of the current state of acupuncture for neurogenic bladder due to SCI. It may provide benefits and clinical evidence for both patients and clinicians.

Although a related systematic review has been published by Hao and colleagues, it still remains uncertain whether acupuncture is an effective and safe therapy for neurogenic bladder due to SCI.[28] In that review, the deadline for study retrieval and selection was September 2012. Only eight studies were selected and there was no verification process (five of the studies were included in meta-analyses). The outcome measures only consisted of urodynamic tests and effective rate. The diversity, validity and reliability of the measures made it difficult to conduct meta-analyses. In addition, the included studies had significant heterogeneity. As a result, no definite conclusion could be reached because of the design defects of the included studies and the small number of studies analysed in the meta-analyses. Moreover, the included studies provided no data which could be used for assessing safety. Therefore, there are some major differences between the review of Hao *et al* and our planned systematic review. First, the number of published RCTs of acupuncture for neurogenic bladder due to SCI has increased since 2012. More studies may be included in this systematic review. Second, following the statement of the International Committee of Medical Journal Editors (ICMJE) published in 2004, which requires that all clinical trials be registered in order to improve the transparency and credibility of clinical evidence,[30] the authenticity of each included study will be checked by searching relevant published protocols and contacting the first or corresponding author. Despite recent increased publicity, some researchers still ignore the importance of trial registration, especially in China. Therefore, it is necessary to verify the authenticity of included studies in order to reduce bias. Third, the outcome measures of our planned review will include differences in urodynamic tests, but will also focus on changes in urinary symptoms, in clinical assessment and in patients' QoL. In addition, the incidence of adverse events will also be assessed as a safety outcome.

Nevertheless, this systematic review will still have some limitations. As an important branch of TCM, acupuncture therapy is classified and denominated according to the type of manipulation and needling instrument. As a result, interventions vary greatly, which increases the difficulty of subgroup analysis. A large number of subgroups will reduce the comparability of studies and increase the complexity of meta-analysis, which may in turn lead to the wrong conclusion. In addition, studies will be obtained from the databases list in the protocol. Because of the language barrier, Korean and Japanese medical databases will not be covered and some relevant studies might be missed.

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Collaborator Ines Eisner-Janowicz.

Contributors HL: planned the protocol; LW: assisted in protocol design; ZL, LW: provided clinical advice on the study protocol; ZL: devised the search strategy; TZ, HL: drafted the protocol; TZ, HL: will search for studies, and extract and analyse data.

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Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement The findings of this systematic review will be disseminated via peer-reviewed publications and conference presentations. All of the data will be available.

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