Acupuncture for gait disturbance of patients with subacute and chronic stroke: a systematic review and meta-analysis protocol

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ABSTRACT
Introduction Hemiparetic gait is one of the most common sequelae of a stroke. Acupuncture has shown potential in correcting hemiplegic gait patterns and improving motor function recovery after stroke. However, controversial findings and a lack of supportive evidence on the effectiveness of acupuncture for post-stroke hemiplegia. The intelligent gait analysis system provides a new perspective for the study of hemiparetic gait. This systematic review aims to collect relevant studies and critically evaluate the efficacy and safety of acupuncture in alleviating gait disturbance of post-stroke hemiplegia based on quantified gait parameters.

Methods and analysis A comprehensive search of PubMed, Embase, Cochrane stroke group trials register, Cochrane Central Register of Controlled Trials, CINAHL, AMED, three Chinese databases (Chinese Biomedical Literatures database (CBM), National Knowledge Infrastructure (CNKI), and Wan fang Digital Periodicals), four trials registries (The WHO International Clinical Trials Registry Platform, The Chinese Clinical Trial Registry, The US National Institutes of Health Ongoing Trials Register, and The Australian New Zealand Clinical Trials Registry) will be conducted to identify randomised controlled trials of acupuncture for gait disturbance in post-stroke patients. No restrictions on language or publication status. The primary outcomes are gait temporospatial parameters (eg, step length, stride length, step width, step frequency), walking speed, etc), and gait kinematic parameters (eg, hip peak flex/extend angle, knee peak flex/extend angle, ankle peak dorsi/plantar-flexion angle, etc). We will assess bias using the approach recommended by the Cochrane Handbook for Systematic Reviews of Interventions. A meta-analysis will be conducted to synthesise the evidence for each outcome measure. The χ² test and I² statistic will be used for assessing heterogeneity between studies.

Ethics and dissemination No ethical approval is needed because no primary data is collected. Scientific conferences or peer-reviewed journals will publish the findings.

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INTRODUCTION
Description of condition Stroke is the second leading cause of death worldwide, and a major cause of adult disability. Motor dysfunction, including a hemiplegic gait disturbance, is one of the most common sequelae of a stroke, which limits the activities of daily living of patients and their participation in community-based activities.

Studies show that 60%–80% of stroke survivors suffer from walking dysfunction. In patients who regain independent walking, their gait efficiency and speed are often persistently reduced when compared with healthy adults. So, recovery of balance and walking function is the main goal of post-stroke rehabilitation. For decades, researchers have studied hemiplegic gait to develop methods for gait analysis and rehabilitation.

Description of post-stroke gait analysis Hemiparetic gait patterns after stroke are a mixture of deviations and compensatory movements. The conventional gait assessment tools, including the Fugl-Meyer Assessment (FMA) scale, the Functional Ambulation Category (FAC) scale and the Tinetti Balance and Gait Analysis, are the
most commonly used outcome measures in clinical trials. However, compared with these conventional gait assessment tools, it is believed that the emerging gait analysis system exerts more objective and accurate data, as well as more reliable results.\textsuperscript{10–11}

A gait analysis system generally refers to a motion capture and analysis system aided by artificial intelligence technology, which examines a subject’s walking pattern systematically to determine their functional level.\textsuperscript{12} A hemiparetic gait pattern can be decomposed into abnormal temporospatial parameters, kinematics parameters, and muscle activities, which are variables possible to be analysed quantitatively.\textsuperscript{16} Studies showed that hemiparetic gait patterns show asymmetry characteristics,\textsuperscript{13} which are defined as shortened stride length, decreased single leg support time, decreased hip/knee peak flexion angle of the paretic side, and overall slowed cadence and walking speed.\textsuperscript{14–15} The invention of the gait analysis system makes hemiparetic gait analysis more efficient and accurate.\textsuperscript{16}

\textbf{Description of intervention}

Recent evidence suggests that acupuncture can be effective in treating cerebrovascular disease.\textsuperscript{17–18} The WHO has proposed that stroke and its sequelae are the main indications for acupuncture.\textsuperscript{19} There are systematic reviews conducted recently suggested that acupuncture therapy is effective and safe for patients with flaccid and spastic hemiplegia after stroke based on conventional gait assessment tools.\textsuperscript{20–21} Randomised controlled trials (RCTs) found that acupuncture improved the balance and lower limb motor function of patients with hemiplegia after stroke.\textsuperscript{17–23} A study of 134 subacute phase stroke participants compared acupuncture plus conventional treatment with conventional treatment only, with 24 sessions of acupuncture therapies and 3-month follow-up, and the result revealed that acupuncture may promote motor function recovery mainly by enhancing the lower limb ability and diminishing the compensation strategies earlier to correct the abnormal gait pattern.\textsuperscript{24}

\textbf{How acupuncture might work?}

A literature review suggested that potential mechanisms of acupuncture effects on stroke include the following aspects: promotion of neurogenesis and cell proliferation in the CNS, regulation of cerebral blood flow, anti-apoptosis and regulation of neurochemicals.\textsuperscript{19} Another review based on MRI revealed that acupuncture could reorganise the motor-related network of post-stroke, including the primary motor cortex (M1), premotor cortex and supplementary motor area.\textsuperscript{23} Recent clinical studies\textsuperscript{26–28} showed that acupuncture could alleviate post-stroke muscle spasticity of affected side limbs. An RCT also showed that acupuncture combined with biofeedback therapy can improve the tibialis anterior muscle strength of the affected limb in hemiplegic patients.\textsuperscript{29}

\textbf{Why it is important to do this review?}

Although some researches support that acupuncture can be effective and safe for post-stroke hemiplegia, a firm conclusion cannot yet be drawn due to controversial results of acupuncture therapy improving walking performance in patients who had a stroke. An updated Cochrane review and meta-analysis in 2016 of acupuncture for stroke rehabilitation announced that insufficient evidence proves acupuncture therapy enhances motor function recovery of patients with subacute stroke.\textsuperscript{1}

Besides, existing studies with controversial outcomes are mostly based on conventional gait assessment tools. We believe that a meta-analysis of studies that use quantitative gait parameters as outcome indicators can draw a conclusion with a higher level of evidence. To our knowledge, several RCTs of acupuncture for hemiparetic gait based on gait analysis systems have been reported and favour of positive results recently,\textsuperscript{30–31} and our preliminary searches of the PubMed database (December 2022) identified about 144 clinical trials.

\textbf{Objectives}

To evaluate the effects and safety of acupuncture on after-stroke motor rehabilitation based on quantitative gait parameters measured by the gait analysis system.

\textbf{METHODS}

\textbf{Types of studies}

RCTs comparing acupuncture therapy for post-stroke gait disturbance with sham acupuncture, and conventional therapy (balance training, gait training, posture transfer training, transcranial magnetic stimulation, muscular low-frequency electrical stimulation, etc.). No language restrictions. Outcome measures without quantitative gait parameters data will be excluded.

To confirm that the trial was indeed randomised, we will contact the study authors if the study report does not describe how it was randomised.

\textbf{Types of participants}

In this review, we plan to include participants who suffer from hemiplegia with subacute (1–3 months since onset) or chronic (over 3 months since onset) phase stroke, both ischaemic and haemorrhagic stroke are taken into consideration. A stroke must have been diagnosed according to the diagnostic criteria for cerebral infarction or intracerebral haemorrhage. No sex, age or race limitation.

This review only focuses on participants with gait disturbance after stroke, and any gait abnormalities (ie, ataxia) or motor deficit caused by other diseases will be excluded.

\textbf{Types of intervention}

Interventions will include any type of acupuncture therapy, such as body acupuncture, scalp acupuncture, electroacupuncture, etc. Control interventions will include sham acupuncture, an inactive intervention or conventional rehabilitation therapy (balance training,
gait training, posture transfer training, transcranial magnetic stimulation, robotic gait training, muscular low-frequency electrical stimulation, etc).

Moreover, we will include studies that compare acupuncture with other active therapies versus those therapies alone.

Trails in which mechanical pressure, laser and electrical stimulus on acupoints without needling as trial group interventions will be excluded. No studies will be included that compare the effectiveness of two different types, dosages or protocols of acupuncture.

Possible comparisons of interest may include:
1. Acupuncture versus sham acupuncture.
2. Acupuncture versus conventional therapies.
3. Acupuncture combined with other active interventions versus other active interventions alone.
4. Acupuncture versus medication treatment only.

Types of outcome measures
We will include trials that applied at least one of the following primary measures via intelligent gait analysis systems.

Primary outcomes
1. 
   Gait temporospatial parameters
   - step length, stride length, step width, step frequency (cadence), walking speed and gait cycle. As well as single limb support time and percentage, double limb support time and percentage, and swing phase time and percentage.
2. Gait kinematic parameters
   - hip peak flex/extend angle, hip peak abduct/adduct angle, hip peak internal/external rotation angle, knee peak flex/extend angle, ankle peak dorsi/plantar-flexion angle.

Secondary outcomes
1. FMA scale.
2. FAC scale.
3. Tinetti Balance and Gait Analysis.
4. Barthel index.
5. Number and type of adverse events (ie, acupuncture tolerance, local bleeding, fainting, infection, etc).

Patient and public involvement
No patient or public involvement.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Electronic searches
The following databases will be searched for relevant trials.
1. PubMed (to the present) (see online supplemental file for draft search strategy).
2. Embase (from 1974 to the present).
3. The Cochrane stroke group trials register (to the present).
4. Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, to the present).
5. CINAHL (to the present).
6. AMED (the Allied and Complementary Medicine Database, to the present).
7. Chinese Biological Medicine Database (from 1978 to the present).
8. China National Knowledge Infrastructure (from 1994 to the present).
9. Wan fang Digital Periodicals (from 1985 to the present).

Searching other resources
1. The WHO International Clinical Trials Registry platform.
2. The Chinese Clinical Trial Registry (www.chictr.org.cn).

Additionally, further published and unpublished trials will also be checked in the references of all relevant articles identified, including reviews.

DATA COLLECTION AND ANALYSIS

Study selection
Potentially relevant article titles, abstracts, or full text will be reviewed independently by two reviewers (ZS and YL) based on the predetermined criteria. In the event of disagreement between authors, a third author (J-YL) will be consulted for consensus. This flowchart (figure 1) summarises the Preferred Reporting Items for Systematic Reviews and Meta-Analyses selection process.

Data extraction and management
The following details of included studies will be extracted using a pre-piloted data extraction form by two authors (ZS and YL) and validated by a third author (K-YH):

Participants: number of participants randomised and analysed; mean age, gender ratio, diagnostic criteria, stroke types and duration, stroke severity, baseline motor impairments.

Methods: study design and setting, recruitment method, inclusion and exclusion criteria.

Intervention: description of acupuncture interventions, containing the type of acupuncture, acupoints selection, total duration of acupuncture treatment, the frequency, duration, number of treatment sessions and follow-up time points.

Comparator: description of control interventions, including forms of interventions, the frequency, duration, number of treatment sessions and total duration of treatment.

Outcomes: outcome measures, including temporospatial parameters, kinematics parameters, functional assessment scales, and type and number of adverse events (ie, acupuncture tolerance, local bleeding, fainting, infection, etc).

Whenever required data from the trials are not available, the primary investigators will be contacted.
Bias assessment of included studies
The risk of bias in included studies will be assessed independently by two authors (ZS and YL) using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the RoB 2 tool for every study.

We will evaluate the following bias categories.
1. Bias arising from the randomisation process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

In addition to the bias described above, we will describe any important concerns that we have about other possible sources of bias. For example, did the design of the study contribute to bias? Is there a claim that the study was fraudulent? Was there a significant imbalance in the baseline?

The bias judgments of each domain will be: ‘low risk of bias’, ‘some concerns’ or ‘high risk of bias’. For each trial, we will consider the risk of bias as follows.

Low risk of bias
The study is judged to be at low risk of bias for all domains for this result.

Some concerns
We had some concerns for at least one domain for this result, but judged none of the domains at high risk of bias.

High risk of bias
A high risk of bias is detected in at least one domain, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Assessment of bias in conducting the systematic review
Any deviations from this protocol will be reported under differences between protocol and review.

Measures of treatment effect
The outcome measures in our statistics are all continuous variables. We plan to evaluate the treatment effect by analysing the mean difference (MD) if similar measure methods are used and gait parameters are in the same units, or standardised MD (SMD) if measure methods or gait parameters units are different, and 95% CIs. As for secondary outcome measures, MD will be analysed if the same scale is used to assess an outcome, or SMD if different scales are used to assess a conceptual outcome, and 95% CIs.

Unit of analysis issues
If there are more than two eligible intervention arms or control arms in one study, we will only report the relevant arms. We will follow one or more of the following methods: identify two or more groups in the shared group and make two or more comparisons; or compare two or more correlated variables and allow for correlations, as described in Chapter 23 of the Cochrane Handbook for Systematic Reviews of Interventions.

Dealing with missing data
Investigators and study sponsors will be contacted to verify key study characteristics and obtain missing or incomplete outcomes data.

Assessment of heterogeneity
A qualitative assessment of clinical heterogeneity between studies will be conducted. We will assess the presence of statistical heterogeneity using the $\chi^2$ test for studies considered sufficiently clinically homogeneous to incorporate into a meta-analysis. $P=0.10$ is considered statistically significant heterogeneity.

According to the $I^2$ statistic, heterogeneity accounts for a greater share of the variance than chance. The following are recommended thresholds for the interpretation of $I^2$ percentages:
1. 0%–40%: might not be important.
2. 30%–60%: may represent moderate heterogeneity.
3. 50%–90%: may represent substantial heterogeneity.
4. 75%–100%: considerable heterogeneity.

Based on the forest plot observations, we will determine whether the $I^2$ statistic is important given the range and direction of effects, and the strength of evidence for heterogeneity according to the $\chi^2$ test. Furthermore, subgroup analyses will be used to examine clinical heterogeneity.
We will report identified substantial heterogeneity, and follow the recommendations in Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions to investigate possible causes.

**Assessment of reporting biases**

To assess the potential for small study bias in meta-analyses that include at least 10 studies, we will use Egger’s test and funnel plots. Furthermore, our assessment of bias will also include an evaluation of the possibility of selective outcome reporting.

**Data synthesis**

A meta-analysis will be conducted across included trials in which sufficient and comparable treatments, population and outcome data are available. We will group all subtypes of gait parameters (e.g., step length, step width, cadence, peak ROM of hip, knee and ankle). We will also perform subgroup analyses of different styles of acupuncture therapies if the data permit (e.g., body acupuncture, scalp acupuncture, electroacupuncture).

The Cochrane Review Manager software (RevMan V.5.4.1) will be used for statistical analyses. One author (ZS) will import data into the software and this will be reviewed by a second author (YL). A pooled MD will be presented with a 95% CI when continuous outcomes are measured similarly and gait parameters are in the same units across studies; SMD estimates will be pooled when studies measure the same outcome using different methods or units. If the I² statistic exceeds 50%, heterogeneity is considered substantial, and a random-effect model will be applied. Otherwise, we will use a fixed-effect model.

In case a small number of studies or significant heterogeneity between studies make pooling data inappropriate, we will present a narrative description of study characteristics and findings under the Synthesis Without Meta-analysis guideline.

**Subgroup analysis and investigation of heterogeneity**

Because effect modifiers influence the effectiveness of interventions in affecting outcomes, we plan to perform the following subgroup analyses:

1. Different types of acupuncture stimulation (manual acupuncture, electroacupuncture).
2. Different sites of needling (scalp acupuncture, body acupuncture, auricular acupuncture).
3. Overall treatment time (4 weeks, 8 weeks, more than 8 weeks).
4. Disease duration (less than 3 months, 3–6 months, more than 6 months).
5. Types of stroke (ischaemic or haemorrhagic).
6. Different stroke severities and baseline motor impairments.
7. Different follow-up durations (3 months, 6 months, more than 6 months).

Our subgroup analyses will focus on primary outcomes that have been measured in at least two studies. For each factor between two or more subgroups, we will use the I² statistic to determine the percentage of the variability in effect estimates that can be attributed to genuine subgroup differences. Based on between-study differences, we will be cautious in drawing conclusions, as advised in Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions.

**Sensitivity analysis**

We will conduct a sensitivity analysis if there is available data for the primary outcomes in the review to determine whether the conclusions are firm. The following factors are examined:

1. A comparison of all trials versus low-risk trials.
2. Reanalyse data with estimates from some studies with less certain results.
3. Using different statistical analysis methods (e.g., random-effect model versus fixed-effect model).
4. Using adjusted endpoint outcome variables versus unadjusted outcome variables.

**‘Summary of findings’ table and evidence quality grade**

We will create a summary of findings (SoF) table, as recommended in the guidelines in Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions. A separate SoF table will be prepared for each comparison. A summary of the evidence for the following outcomes will be included in the SoF table:

1. Gait temporospatial parameters (e.g., step length, step width, step frequency, walking speed and gait cycle).
2. Gait kinematic parameters (e.g., hip peak flex/extend angle, knee peak flex/extend angle, ankle peak dorsi/plantar-flexion angle).
3. Walking ability assessment scales (e.g., FMA, FAC, Tinetti Balance and Gait Analysis).
4. Adverse events (i.e., acupuncture tolerance, local bleeding, fainting, infection, etc).

We will assess the evidence level using Grading of Recommendations Assessment, Development and Evaluation (GRADE) by two review authors (ZS, KS) independently. The GRADE methods and recommendations described in Chapters 14 and 15 of the Cochrane Handbook for Systematic Reviews of Interventions will be followed.

**DISCUSSION**

The purpose of this protocol is to outline a rigorous, methodical approach to conduct a systematic review to evaluate the effects and safety of acupuncture on post-stroke motor rehabilitation based on quantitative gait parameters measured by the gait analysis system.

Among included studies, these gait analysis systems do not need to be of the same production specification, which can help us expand the sample size. It can be a gait analysis laboratory with several cameras in specific directions, or a wearable sensor device through a wireless
connection to a computer, or an equipment that uses infrared sensing, etc, which all finally export data through adapted computer software.

A recent study showed that walking speed and stance-phase time in hemiplegic patients are related to ambulatory and balance functions. Gait parameters are the elements that make up a walking pattern. Changes in gait parameters also mean changes in walking patterns. For example, for patients with hemiparetic gait pattern, the increase of the maximum hip and knee flexion angles, or the increase of maximum ankle dorsiflexion angles of the affected limbs indicates improvement of the foot clarification ability; the increase in step length and step frequency of the affected limb represents the enhancement of walking efficiency, which can explain that changes in gait parameters can reflect the improvement of patients’ walking function. Although gait parameters are the main outcome indicators, the functional scales (secondary outcomes) are still an important part of our final comprehensive analysis, because they are the connecting points to interpret the estimated effects from a clinical perspective.

Based on current evidence, it is uncertain whether acupuncture improves gait function in hemiplegia. On this basis, we will summarise updated studies that set gait parameters as main outcome indicators, and simultaneously incorporate conventional functional scales to provide more comprehensive evidence by conducting a systematic review and meta-analysis.

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