INPLASY

Traditional Chinese medicine therapy for treating amyotrophic lateral sclerosis: a Bayesian network meta-analysis

INPLASY202480050

doi: 10.37766/inplasy2024.8.0050

Received: 08 August 2024

Published: 08 August 2024

Shen, C; Wu, XT; Zhang, CH; Yin, H; Cao, F; Zuo, JL; Robinson, N; Liu, JP.

Corresponding author:
Jian-Ping Liu

liujp@bucm.edu.cn

Author Affiliation:
Beijing University of Chinese Medicine; London South Bank University.

ADMINISTRATIVE INFORMATION

Support - Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No: ZYYCXTD-C-202006).

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202480050

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 August 2024 and was last updated on 08 August 2024.

INTRODUCTION

Review question / Objective Does traditional Chinese medicine alone or in combination with conventional medicine provide therapeutic benefit for adults with amyotrophic lateral sclerosis?

Condition being studied Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons in the brain, brainstem, and spinal cord. This results in muscle weakness and atrophy that progresses rapidly, eventually leading to paralysis and death within 2 to 5 years from the onset of clinical symptoms. ALS can be classified into two main types: familial (fALS) and sporadic (sALS). While fALS accounts for only about 5-10% of all cases, it often has a genetic component with autosomal dominant inheritance patterns. The pathogenesis of ALS remains largely unknown, but genetic mutations, environmental and lifestyle factors may play roles in the development of sALS. In approximately 20% of cases, a genetic mutation can be identified as the underlying cause. With the introduction of molecular therapies targeting specific genetic subtypes of ALS, there is an increasing agreement to provide rapid genetic testing for all individuals diagnosed with ALS.

The primary goal of current ALS treatment is to manage symptoms and improve quality of life rather than cure of the disease. The U.S. Food and Drug Administration has approved four drugs for ALS: riluzole, edaravone, relyvrio, and tofersen. However, the first three treatments are modestly effective and do not reverse or stop the progression of ALS. Tofersen, on the other hand, has shown promise in slowing down the disease's progression in patients with SOD1 mutations but has not been applied to all patients. Traditional Chinese medicine (TCM) has been used historically

to treat various neurological conditions through herbal medicines and non-pharmacological interventions. According to a cross-sectional survey in Shanghai, China, over 99% of patients with ALS use integrative therapies, with herbal medicine being utilized by 40% of patients in America. The most frequently employed integrative therapies in China include vitamins, Chinese herbal decoctions, Chinese herbal compounds, massage therapy, and acupuncture. Previous studies have demonstrated that Chinese herbal medicine (CHM) outperformed placebo in increasing ALS Functional Rating Scale (ALSFRS) scores after 3 months of treatment, as well as riluzole after 4 weeks of treatment. Additionally, CHM showed superiority over conventional medicine (CM) alone when used as an adjunct therapy after 8 weeks of treatment. Among CHMs, to delay activity limitation, Jiweiling injection and Shenmai injection showed significantly greater effectiveness compared to Riluzole. Jiweiling injection was also demonstrated effect for ameliorating motor neuron loss.

METHODS

Participant or population Adults with age over 18 years who were diagnosed with ALS will be included. Diagnostic criteria based on any version of the consensus criteria, such as the El Escorial criteria (2000), Awaji algorithm (2008), or Gold Coast criteria (2020), will be considered acceptable. Adapted diagnostic criteria based on these standards, commonly employed in various countries, will be also permissible. There is no restriction on the age, race, or gender of the participants.

Intervention Traditional Chinese medicine therapies can be employed either independently or as adjunctive therapy alongside conventional medicine. These interventions encompass herbal medicine or preparations, as well as non-pharmacological approaches like acupuncture or massage. There are no specific restrictions regarding the dosage or formulation of herbal medicines.

Comparator Eligible control therapy includes one or a combination of a placebo, no treatment and conventional medicine.

Study designs to be included Parallel group, randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs) regardless of blinding or publication types. Cross-over trials will also be included if the first round data of outcomes are reported before cross-over.

Eligibility criteria There is no limitation in the study context, community or hospital-based.

Information sources We will search the following electronic databases from their inception to 9th August 2024: Pubmed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang database, Chinese Scientific Journal Database (VIP) and Chinese biomedical literature database (CBM). We will also hand-search the reference lists of all full-text papers for additional relevant reports. Searches will be limited to randomized controlled trials and non-randomized controlled trials in all languages.
Details of the search strategy will be available from the authors on request.

Main outcome(s) The primary outcome includes functional status assessed using the ALS functional rating scales (ALSFRS) or the revised ALS functional rating scales (ALSFRS-R), Appel ALS Score (AALSS) or the modified Norris scale (m-Norris).

Additional outcome(s) The secondary outcomes include:
1) Survival time, including tracheostomy-free survival or overall survival. Tracheostomy-free survival is defined as time to death, tracheostomy, or permanent non-invasive positive pressure ventilation.
2) Quality of life: Assessed using specialized scales such as the ALS Specific Quality of Life Instrument (ALSSQOL), ALS Assessment Questionnaire-40 (ALSAQ-40) or general scales such as the MOS Item Short-form Health Survey (SF-36) or the Barthel index.
3) Respiratory Function: Measured using Vital Capacity (VC) or Forced Vital Capacity (FVC).
4) Symptom improvement or relief measured by validated scales or instruments.
5) Motor neuron loss: Assessed via motor unit number estimation (MUNE) or other neurophysiological tests.
6) Cognitive and behavioral impairment: Measured using tools such as the ALS Cognitive Behavioral Screen (ALS-CBS).
7) Adverse events.

Data management After removing duplicates of the identified studies, six authors in pairs (C Shen, XT Wu, CH Zhang, H Yin, F Cao, JL Zuo) will screen the studies independently. The first round of screening will be based on reading titles and abstracts, subsequently followed by full-text screening. The discrepancies will be resolved through consensus and if necessary, arbitrated by

another author (JP Liu). Then six authors in pairs independently will extract data from the included studies according to a predesignated extraction table.

Quality assessment / Risk of bias analysis The Cochrane Risk of Bias 2.0 (RoB 2.0) and Robins-I will be respectively employed to evaluate the methodological quality of included RCTs and non-RCTs. The six authors in pairs will independently assess the quality and consensus will be reached by discussion with a third party (Liu JP) in case of discrepancy. Five areas will be assessed in RoB 2.0: bias generated in the random process, bias deviating from the established intervention, bias of missing outcome data, bias of outcome measurement and bias of selective reporting of results. Seven domains will be assessed through Robins-I: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Disagreements will be resolved by discussion with a third party (JP Liu).

Strategy of data synthesis Using direct or indirect comparisons and cumulative ranking probability, network meta-analysis can be evaluated for relative advantages and disadvantages. This study will be based on the Bayesian network meta-analysis and use R 4.4.0. A risk ratio (RR) with a 95% confidence interval (CI) will be calculated for dichotomous variables. In the case of continuous variables, we will calculate the mean difference (MD) with 95% CI. We will use the I2 test and $\chi 2$ test for heterogeneity. All effect size will be analyzed using a random effect model because it gives similar weights to studies with different sample sizes and substantial heterogeneity would be expected between studies. If the data fails to meet the condition of meta-analysis, we will synthesis the data narratively. In cases where the diagram contained a closed loop, the inconsistency test will be used to evaluate the consistency between the results of direct and indirect comparisons. In the absence of a closed loop, the consistency model will be directly used for analysis. Each outcome will be ranked using the surface under the cumulative ranking curve (SUCRA), with a greater SUCRA value indicating a better effect.

Subgroup analysis We will perform subgroup analyses based on different pattern of Chinese medicine syndrome, different comparisons of interventions, and randomized and non-randomized studies.

Sensitivity analysis To test the robustness of the results, trials with low risk of bias in participant allocation and blinding will be included for sensitivity analysis.

Country(ies) involved China, The United Kingdom.

Keywords Traditional Chinese medicine; amyotrophic lateral sclerosis; ALS; motor neuron disease; systematic review; Bayesian network meta-analysis.

Contributions of each author

Author 1 - Chen Shen.
Email: shenchensophia@bucm.edu.cn
Author 2 - Xiao-Ti Wu.
Email: xiaoti2409@163.com
Author 3 - Chen-Hao Zhang.
Email: zchh1208nn@163.com
Author 4 - Heng Yin.
Email: 20200621018@bucm.edu.cn
Author 5 - Feng Cao.
Email: feng@bucm.edu.cn
Author 6 - Jing-Ling Zuo.
Email: 16673408920@163.com
Author 7 - Nicola Robinson.
Email: prof.nicky.robinson@outlook.com
Author 8 - Jian-Ping Liu.
Email: liujp@bucm.edu.cn