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None declared.

Traditional Chinese medicine non-pharmacological interventions for Lumbar Disc Herniation: a systematic review and network meta-analysis of randomized controlled trials

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Review question / Objective: **This systematic review and network mata-analysis of randomized controlled trials is aimed to evaluate the efficacy and safety of TCM non-pharmacological interventions for patients with lumbar disc herniation (LDH).**
Information sources: **PubMed, EMBASE, Cochrane library, China National Knowledge Infrastructure (CNKI) and grey literature will be searched from inception to March 31,2021. If the required data is lost or incomplete, we will contact the corresponding author or the first author by e-mail or http://www.researchgate.net. If there is no response, the record is excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 April 2021 and was last updated on 23 April 2021 (registration number INPLASY202140117).

INTRODUCTION

Review question / Objective: **This systematic review and network mata-analysis of randomized controlled trials is aimed to evaluate the efficacy and safety of TCM non-pharmacological interventions for patients with lumbar disc herniation (LDH).**

Rationale: **Lumbar disc herniation (LDH) refers to a syndrome of lumbar or leg pain caused by partial or complete rupture of annulus fibrosus and protrusion of nucleus pulposus alone or together with annulus**

fibrosus cartilage endplate after degenerative disease of lumbar disc, stimulating or compressing sinus and vertebral nerves and nerve roots. It is a common disease that influences patients' physical function, quality of life, and carries an enormous financial burden on patients. It is estimated that chronic low back pain (CLBP) worldwide prevalence was 19.6% in those aged between 20 and 59, and increases linearly from 30 until the 60 years of age. Within the vast differential of low back pain, the most common source is intervertebral degeneration leading to degenerative disc disease and LDH. Multiple studies have shown that the incidence of lumbar disc herniation is 2%-3%, among which the incidence of women over 35 years of age accounts for about 2.5%, and that of men accounts for about 4.8%. Thus, an effective and appropriate therapy of LDH is of substantial importance.

Condition being studied: Treatments for patients with lumbar disc herniation include both operative and non-operative managements. Surgical intervention should be considered when conservative treatment fails to prevent or ameliorate pain or nerve damage symptoms caused by further exacerbation of lumbar disc herniation, and approximately 10% to 20% of patients will eventually require surgical treatment. However, the efficacy of surgical treatment is controversial to some extent, in mid-term and long-term follow-up after surgery, surgical treatment did not show a benefit over conservative treatment. What's more, persistent radiculopathy after surgical treatment for LDH affects the rehabilitation of patients and the possibility of re-operation. Therefore, non-operative treatment has become a trend. Traditional Chinese medicine (TCM) treatment is one part of non-operative treatment, as a main component of complementary and alternative medicine (CAM), it has been widely applied in management of LDH. Compared to surgical treatment and pharmacotherapy, TCM is safe and economical. TCM covers numerous therapies, including acupuncture, moxibustion, cupping, tui na, traditional Chinese exercise (e.g. tai chi, qigong, ba duan jin), etc. Several studies have demonstrated the efficacy of TCM in patents with LDH. However, as the traditional meta-analysis can only carry out pair comparison and does not involve the comparison between multiple therapeutic measures, network meta-analysis is an extension of the traditional meta-analysis, which has the advantage of being able to evaluate the efficacy of multiple interventions. Although Mo et al had designed a network meta-analysis to compare the efficacy of tuina, acupuncture, traction, and Chinese herbs for LDH, only four outcomes were analyzed in their research, and the TCM interventions they compared were limited, we cannot choose the best appropriate between multiple types of interventions. On this basis, it is necessary to carry out and update such a network meta-analysis to provide an evidence for clinical practice by comparing the efficacy of multiple TCM non-pharmacological interventions.

METHODS

Search strategy: An electronic search of PubMed, EMBASE, Cochrane library, China National Knowledge Infrastructure (CNKI) will be undertaken from inception to March 31, 2021. Mesh tems and key words will be used to identify RCTs with the limitation of English and Chinese language. In addition, inclusive literature from the field and references from previous evaluations will be manually retrieved to find other potentially relevant articles. Search strategy for PubMed: #1 “lumbar vertebrae” (Mesh); #2 “intervertebral disc disease” (Mesh); #3 “intervertebral disc degeneration”(Mesh); #4 “intervertebral disc displacement”(Mesh); #5 lumbar disc disease (Title/Abstract); #6 disk, herniated (Title/Abstract); #7 herniated disk (Title/Abstract); #8 herniated disc (Title/Abstract); #9 slipped disc (Title/Abstract); #10 slipped disk (Title/Abstract); #11 disc herniation (Title/Abstract); #12 disk herniation (Title/Abstract); #13 disc prolapse (Title/Abstract); #14 disk prolapse (Title/Abstract); #15 lumbar (Title/Abstract); #16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14); #17 (#16 AND #15); #18 "Medicine, Chinese Traditional" (Mesh); #19 acupuncture (Mesh)#20 electroacupuncture (Mesh) #21 moxibustion (Mesh); #22 "tai ji" (Mesh); #23 Qigong (Mesh); #24 massage (Mesh); #25 "cupping therapy"(Mesh); #26 traction (Mesh); #27 fumigation (Mesh); #28 "traditional Chinese medicine" (Title/Abstract); #29 needle (Title/Abstract); #30 moxabustion (Title/Abstract); #31 "tai chi" (Title/Abstract); #32 "Wu qin xi" (Title/Abstract); #33 "Wuqinxi" (Title/Abstract); #34 "Ba duan jin" (Title/Abstract); #35 "traditional Chinese exercise" (Title/Abstract); #36 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35); #37 (#36 AND #17); #38 ("randomized controlled trial" (filters) OR clinical trial (filters) OR randomized (tiab)); #39 humans (filters); #40 (#38 AND #39); #41 (#37 AND #40).

Participant or population: Adult patients (> 18 years) with LDH (consistent with the guideline for the diagnosis and treatment of LDH with radiculopathy)(Kreiner et al., 2014). We will exclude participants who undergo TCM non-pharmacological interventions after lumabr surgery. There will be no restriction on gender, race, disease duration or disease severity.

Intervention: Any kinds of TCM non-pharmacological interventions including acupuncture, moxibustion, cupping, etc. We also include interventions where combine two kinds of TCM non-pharmacological interventions, interventions combing other treatments when the control groups receive the same co-interventions will also be included.

Comparator: Control interventions will include no treatment, sham treatment, drugs or any active treatment. Articles that focus on dose-response relationships with the same interventions will be excluded. Studies comparing the same kind of TCM non-pharmacological interventions, but with different sessions, doses, acupoints will be taken as the identical node in network analysis.

Study designs to be included: This study is a systematic review and network meta-analysis of randomized controlled trials with TCM non-pharmacological interventions on LDH. Only randomized controlled trials (RCTs) with complete and available data will be included, regardless of publication status. The language of these studies will be limited to English and Chinese. We will remove the studies without comparable baselines and duplicate publications.

Eligibility criteria: This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. We will follow the PICOS criteria mentioned above.

Information sources: PubMed, EMBASE, Cochrane library, China National Knowledge Infrastructure (CNKI) and grey literature will be searched from inception to March 31,2021. If the required data is lost or incomplete, we will contact the corresponding author or the first author by e-mail or http://www.researchgate.net. If there is no response, the record is excluded.

Main outcome(s): The primary outcome of this study is pain intensity (e.g. Visual Analogue Scale or Numerical Rating Scale) or functional disability (e.g. Oswestry Disability Index or Japanese Orthopedic Association Scores or Roland Morris Disability Questionnaire).

Additional outcome(s): Secondary outcomes. Health-related quality of life (e.g. the 36-item Short-Form Health Survey) or interventions related adverse events.

Data management: We will follow PRISMA 2020 statement to conduct study selection. Two authors (Zhenni Zhao and Rui Zhang) will screen studies according to the inclusion and exclusion criteria. We will conduct a preliminary screening of the literature by software to remove duplication, the second step is to read the

title and abstract to remove the literature that does not meet the inclusion criteria, finally, through obtaining and reading the full text to identify the eligible studies. Two authors (Yun Feng and Yanyan He) will check this process and full text and disagreements will be resolved by consultation with a corresponding author (Zhiling Sun). Data extraction: One author (Zhenni Zhao) will use a standardized table to extract characteristics from studies, including first author, publication year, country, patients, sample size, details of experimental and controlled groups, follow-up time, outcomes, outcome measures. A second author (Yanyan He) will check these information and disagreements will be resolved by consensus. If key information was missing from the study report, we will contact the report authors to obtain the information.

Quality assessment / Risk of bias analysis: Two authors (Rui Zhang and Yun Feng) will assess the risk of bias recommended by Cochrane Handbook of Systematic Reviews of Interventions. We will judge risk of bias as "low", "unclear", "high" on the following domains: selection bias (random sequence generation, allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); other bias (baseline differences, early termination, fund). Based on Cochrane Collaboration's tool, when all the key domains are judged as "low", we judge the overall risk of bias as low. When 1 or more key domains are judged as "unclear", we judge the overall risk of bias as moderate. When 1 or more key domains are judged as "high", we judge the overall risk of bias as high.

Strategy of data synthesis: Network meta-analysis: This study uses ADDIS 1.16.8 based on Bayesian framework for network meta-analysis. Odds ratios (ORs) or standardized mean differences (SMD) will be modeled using Markov chain Monte Carlo methods, both with 95% confidence intervals (CIs). Preset model parameters: 4 chains are used for simulation analysis, with an initial value of 2.5, a step size of 10, 20,000 annealing times, and 50,000 simulation iterations. The network evidence plot will be generated according to different outcome. According to the results of the network meta-analysis, rank probability plot of various TCM non-pharmacological therapies will be generated and sorted by dominance, with Rank1 being the optimal sort. Consistency assessment: Node-splitting model is used to test the consistency between closed loop studies with both direct and indirect evidence, if there is no statistical difference ($P>0.05$), the consistency model is used, whereas the inconsistency model is used for analysis. If the consistency model is adopted, then the stability of the results is verified by the inconsistency model: when the inconsistency factors including 0, at the same time inconsistency standard deviation including 1 says the result of consistency model is more stable and reliable. At the same time, various analysis models are iterated with preset parameters, and the convergence of iteration effect is judged by potential scale reduced factor (PSRF). When the PSRF value is close to or equal to 1 ($1 \leq PSRF \leq 1.05$), the convergence is complete, the model has good stability, and the conclusion of analysis is reliable. If the PSRF value is not in this range, the iteration continues manually until the PSRF value reaches the range standard. Heterogeneity test: Before the combination of effect size, we will use Stata to assess available study and patient characteristics to ensure similarity and to investigate the potential effect of heterogeneity on effect estimates. When inter-study heterogeneity exists, the random effect model is used. For comparison of each pair, heterogeneity is assessed by the statistic I^2 value. When $I^2>50\%$, it indicates that there is heterogeneity between studies, and the source of heterogeneity should be further searched. When $I^2<50\%$, inter-study heterogeneity is considered to be small or there is no obvious heterogeneity.

Subgroup analysis: If necessary, we will conduct a subgroup analysis of duration of

treatment, follow-up time, location, age, control group settings, and research quality.

Sensitivity analysis: If necessary, we will perform sensitivity analyses by using a common approach, where each trial was excluded one by one to check whether the estimate changes, if there is no qualitative change in the combined effect showed in the results, the results are stable.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: TCM, non-pharmacological treatment, lumbar disc herniation, meta-analysis, clinical trial.

Contributions of each author:

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