The efficacy and safety of acupuncture in the treatment of erectile dysfunction: A protocol for systematic review and meta-analysis

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Abstract

Background: Erectile dysfunction (ED) can negatively affect men’s mental health, interpersonal relationships, and overall well-being. ED has affected >150 million men worldwide, and this number will reach approximately 322 million by 2025. Although PDE5-Is is a landmark in the treatment of erectile dysfunction, it may have side effects such as penile pain, cardiovascular dysfunction, and deafness. Some studies have shown that acupuncture may have a positive effect on the pathophysiology of ED. Therefore, we will select all randomized controlled trials related to evaluate the efficacy and safety of acupuncture treatment of ED.

Methods: This study will systematically search 7 digital databases including China National Knowledge Infrastructure, Wanfang, VIP, China Biology Medicine, Cochrane Library, PubMed, and Embase for randomized controlled trials without language restrictions. Two researchers will independently read the title, abstract, and full text to screen for studies that can be included in the meta-analysis. If there is any dispute, the third party will be required to reach a consensus.

Results: The purpose of this study is to evaluate the efficacy and safety of acupuncture in the treatment of ED and the difference in the impact of different types of acupuncture on ED.

Conclusion: Judge whether acupuncture and moxibustion can help improve the symptoms of ED by evaluating relevant literatures, and make up for the lack of relevant research.

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Abbreviations: ED = erectile dysfunction, DSM = Diagnostic and Statistical Manual of Mental Disorders, RCTs = randomized controlled trials.

Keywords: acupuncture, complementary therapy, efficacy, erectile dysfunction, impotence, TCM

1. Introduction

Erectile dysfunction (ED) is a male disease characterized by difficulty in erecting or maintaining sufficient erection strength for satisfactory sexual performance. Penile erection is accomplished by the regulation of psychological factors and hormonal status. Risk factors for erectile dysfunction include smoking, alcohol, diabetes, depression, metabolic syndrome, and obesity. ED can negatively affect men’s mental health, interpersonal relationships, and overall well-being. Erectile dysfunction has affected >150 million men worldwide, and by 2025, this number will reach approximately 322 million. Ample evidence show that ED is a risk marker for treatable underlying diseases. And if ED is not effectively treated, these diseases will reduce the quality and length of life. In general, oral PDE5-Is is the main drug for the treatment of erectile dysfunction. Other treatments include lifestyle changes, injection therapies, testosterone therapy, penile devices, and psychotherapy. Oral PDE inhibitors are a convenient, effective, and widely available treatment option for erectile dysfunction. Although PDE5-Is is a landmark in the treatment of erectile dysfunction, they are far from perfect. As we all know, the disadvantages of PDE5-Is are the uncommon success rate, absence of spontaneity, and life-long drug commitment. In addition, these therapies are not always effective and may have side effects such as penile pain, cardiovascular dysfunction, and deafness. Currently, specific treatments not only for PDE5 enzyme inhibition are under development. Acupuncture is a component of Traditional Chinese Medicine that can be traced back at least 2500 years. Some studies have shown that the neurophysiological effects of acupuncture, due to...
central nervous system activation and neurotransmitter regulation, may positively affect the pathophysiology of ED.\textsuperscript{[20,21]} In urinary system diseases, acupuncture has been successful as the main or adjuvant therapy for enuresis,\textsuperscript{[22]} bladder instability,\textsuperscript{[23]} and male infertility.\textsuperscript{[24]} Through preliminary retrieval and analysis of database resources, we found that randomized controlled trials (RCTs) of acupuncture treatment in the ED are gradually increasing. Therefore, the purpose of our program is to select all RCTs related to evaluate the efficacy and safety of acupuncture in the treatment of ED in comparison with other drug therapies.

2. Objectives

The aims are to compare the efficacy of acupuncture for the treatment of ED and to analyze the curative effect of different acupuncture interventions on ED.

3. Methods and analysis

3.1. Study registration

The protocol of our study is conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols guidelines and the Cochrane Handbook.\textsuperscript{[25,26]} This protocol has been registered on INPLASY (registration number: INPLASY 202140040: https://inplasy.com/inplasy-2021-4-0040/).

3.2. Inclusion criteria

3.2.1. Type of studies. Only RCTs will be included.

3.2.2. Type of participants. Participants are patients >18 years of age who are diagnosed with ED. ED must be diagnosed by clinical and/or instrumental methods. The diagnosis will be based on the Diagnostic and Statistical Manual of Mental Disorders Third Edition (DSM)-III, DSM-III-R, DSM-IV, International Statistical Classification of Diseases and Related Health Problems (ICD)-10 criteria or any other described criteria.

3.2.3. Type of interventions. The types of acupuncture in the intervention group include: manual acupuncture, electric acupuncture, scalp acupuncture, ear acupuncture, moxibustion, and fire needling.

3.2.4. Type of comparators. Control measures can include: placebo/sham acupuncture or other interventions (such as drugs, physical therapy).

3.2.5. Types of outcome measures

3.2.5.1. Primary outcomes. The main result will be an improvement in sexual activity. This will be assessed through validated questionnaires such as the International Index of Erectile Function.

3.2.5.2. Secondary outcomes. Secondary outcome measures include quality of Life, improvement in anxiety or depression scales, and the rate of adverse effects.

3.3. Exclusion criteria

Exclusion criteria are: non-RCTs; trials using unverified questionnaires or without a clear description of the evaluation method; studies with imbalanced or incomparable baseline data between the 2 groups will be excluded.

3.4. Search methods for identification of studies

3.4.1. Electronic searches. This study will systematically search 7 digital databases including China National Knowledge Infrastructure, Wanfang, VIP, China Biology Medicine, Cochrane Library, PubMed, and Embase for RCTs without language restrictions. The following search terms will be used individually or in combination: acupuncture, electro-acupuncture, Warm Acupuncture, elongated needle, erectile dysfunction, impotence, and ED. Two researchers will independently read the title, abstract, and full text to screen for studies that can be included in the meta-analysis. The searching strategy of PubMed is presented in Table 1.

3.4.2. Searching other resources. We will search the National Institutes of Health clinical registry Clinical Trials, International Clinical Trials Registry Platform, and ClinicalTrials.gov to find any ongoing or unpublished trial.

3.5. Selection of studies

The studies of electronic searches will be exported to EndNote V.9.1 software to remove duplicate literature. Literature screening will be conducted independently by 2 reviewers according to the inclusion and exclusion criteria. They first read the title and abstract of the studies to exclude irrelevant trials. Then they read the full text to further screen out the documents that meet the requirements. Finally, valid data will be extracted in the included literature one by one. If there is a disagreement during the screening process, the final decision will be reached through discussion with the third reviewer. The selection process will be shown in a PRISMA flow diagram (Fig. 1).

3.6. Data extraction and management

Two authors will independently select the trials included in the review according to the inclusion/exclusion criteria. Any
disagreement will be resolved by discussion. We will perform
data extraction using a Microsoft Excel spreadsheet. Information
extracted from each included article will include
first author, publication year, sample size, characteristics of participants, type
of treatments, and outcome measures. If the necessary data are
not available in the trial reports, further information will be
sought by contacting corresponding author.

3.7. Assessment of the methodological quality
The risk of bias in the included literature will be assessed
according to the Cochrane Collaboration’s tool for assessing risk
of bias.[26] We will assess the risk of bias from the following 7
items: random sequence generation, allocation concealment,
blinding of participants and personnel, blinding of outcome
assessment, incomplete outcome data, selective reporting, and

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For more information, visit www.prisma-statement.org.

Figure 1. Flowchart of literature selection.
other sources of bias. The risk of bias graph and the risk of bias summary will be generated by Review Manager (RevMan) V.5.3 software. Any disagreement should be solved in consultation with a third reviewer.

3.8. Measures of treatment effect
For continuous data, the mean difference will be used in the analysis of continuous outcomes with 95% confidence intervals. In case outcome variables have different scales, the standardized mean difference will be used with 95% confidence intervals. The relative risk will be used to assess dichotomous outcomes.

3.9. Dealing with missing data
We will attempt to contact authors to obtain missing data. If we cannot contact the original authors, the studies will be excluded from the data synthesis.

3.10. Assessment of heterogeneity
The Cochran Q statistics will be employed to assess heterogeneity. If there is significant clinical heterogeneity or methodological heterogeneity ($I^2 > 50\%$), the subgroup analysis will be performed to explore sources of heterogeneity. To assess potential bias resulting from baseline risk, we will perform meta-regression with regressors which included age of participants, sample size, duration of disease, course of treatment, and so on. Besides, sensitivity analyses will be performed by excluding studies with a high risk of bias or poor quality to judge the stability of the results.

3.11. Data synthesis
Fixed-effects models will be used if the $I^2$ value is $<50\%$. Otherwise, we will remove low-quality studies and use sensitivity analysis to investigate which study has the most significant impact on heterogeneity. If quantitative synthesis is not possible, we will make a qualitative description.

3.12. Subgroup analysis
If there is significant heterogeneity between the study results, we will perform a subgroup analysis to investigate differences in sex, age, types of acupuncture interventions styles, and so on.

3.13. Sensitivity analysis
Sensitivity analysis will be conducted to explore the effects of trial risk of bias on important outcomes. Several factors in the meta-analysis process will be taken into consideration, such as low-quality research, small sample research, and so on. In addition, we will give the results of the sensitivity analysis in the summary table. The results of the sensitivity analysis will discuss the risk of bias in the meta-analysis.

3.14. Grading the quality of evidence
Two reviewers will independently use the Grading of Recommendations Assessment, Development and Evaluation. According to the grading standard, the quality of evidence is graded as high, medium, low, or very low.

3.15. Ethics and dissemination
The study will be published in a peer-reviewed journal or relevant conference. No ethical approval is required. The results of the study will provide potential evidence in advancing the therapeutic strategy of patients with ED.

4. Discussion
Epidemiological studies have found that the prevalence of ED is high. As the life expectancy of the general population increases, the health care burden and quality of life issues associated with ED are expected to be considerable. The current treatments used for ED include oral drug therapy, intracavernosal injection and implantation of penile prostheses. PDE5-Is is currently used as a first-line treatment for ED. However, there are still a large number of patients who do not respond to this therapy. In addition, implanting penile prostheses is expensive and may cause penile deformities. Therefore, an ideal ED treatment method has not yet been developed. With the increasing use of acupuncture in the treatment of ED, our systematic review aims to evaluate the current evidence of the effectiveness and safety of acupuncture in the treatment of ED and provide other treatment options for ED patients.

Author contributions
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