Effectiveness of acupuncture for nocturia: a protocol for systematic review and meta-analysis

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Abstract
Background: Nocturia is a common and highly troubling condition of the lower urinary tract symptom, which has a wide range of effects. About 33% of patients with lower urinary tract symptoms have been affected by nocturia. Nocturia is mainly manifested as the increase of urination frequency and urine volume at night. It has been proved that acupuncture can reduce the symptoms of nocturia and regulate bladder function in Western countries. Acupuncture may be a promising choice for the treatment of nocturia.

Methods: RCTs of acupuncture for nocturia will be searched in the relevant database, including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure Wanfang Database, Chinese Biomedical Literature Database, and Chinese Scientific Journal Database. The studies of electronic searches will be exported to EndNote V.9.1 software. We will run meta-analyses using the Review Manager (RevMan) V.5.3 software. Any disagreement will be solved in consultation with a third reviewer.

Results: Our study aims to explore the efficacy of acupuncture for nocturia and to provide up-to-date evidence for clinical of nocturia.

Conclusion: The conclusion of this study will provide evidence for the efficacy of acupuncture treatment of nocturia.

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Abbreviations: N-QoL = quality of life, PSQI = Pittsburgh Sleep Quality Index, RCTs = randomized controlled trials.

Keywords: acupuncture, complementary therapy, nocturia, randomized controlled trial, systematic review

1. Introduction

Nocturia is a common and highly troubling condition of the lower urinary tract characterized by increased frequency and volume of urination at night.[1] The International Continence Society,[2] defines it as “the complaint that the individual has to wake at night 1 or more times to void.” Nocturia is widespread in adults, and approximately 33% of patients with lower urinary tract symptoms show that they are affected by nocturia. A retrospective study of the prevalence of nocturia from 1990 to 2009 found that among young adults aged 20 to 40 years, the incidence ranged from 11% to 35.2% in males and 20.4% to 43.9% in females, while the prevalence ranged from 68.9% to 93% in older adults aged 70 years and older.[3]

According to the pathophysiological mechanism of nocturia, its etiology is mainly caused by 4 aspects: nocturnal polyuria, 24-hour polyuria, decreased bladder volume and sleep disturbance.[4] Its occurrence and development are closely related to bladder hyperactivity and lower urinary tract symptoms.[5] The essence is the result of an imbalance between functional bladder storage capacity and urine production.[6] Nocturia is not only characterized by increased nocturnal urination, but also may be associated with the risk of other diseases. Frequent nocturnal awakenings due to nocturia can lead to worse sleep, increased daytime sleepiness, and reduced energy and activity in older adults.[7] Older adults are also at increased risk of falling due to repeated night time bathroom visits. Datas show that[8] 25% of falls in the elderly are directly related to nocturia, and patients who use the night time bathroom at least two or more times per night more than double the risk of fractures and fall-related trauma. Nocturia is also associated with an increased risk of urinary tract disorders such as urethral obstruction, bladder diverticulum, hydronephrosis, and vesicoureteral reflux, as well as an increased prevalence of chronic diseases such as hyperglycemia, diabetes, coronary heart disease, and nervous system.[9-11] It is accompanied by a variety of complications seriously affect the physiological and psychological state of patients, reduce the quality of life (N-QoL) of individuals.[12]

Currently, nocturia is mainly treated with drugs, including

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desmopressin, α1 receptor antagonists, 5α reductase inhibitors, and antimuscarinic drugs. These drugs mainly improve nocturia symptoms by enhancing the kidney’s reabsorption of water during the night, regulate the activity of the brainstem urination center and improve urodynamic. However, drugs often have side effects during treatment. For example, α1 blockers can lead to cardiovascular disease, aggravate heart failure, induce vasodilation-induced lowering of blood pressure, lead to poststatic hypotension, and cause dizziness and falls. Desmopressin tends to cause hyponatremia, and 5-ARI can worsen erectile dysfunction and lower testosterone levels in men. Although some therapeutic measures such as lifestyle regulation, Magnetic stimulation, and botulinum toxin A (BoNT/A) have been used to promote the improvement of nocturia symptoms, the efficacy of these treatments is relatively limited and there is A lack of efficacy data to the treatment of nocturia still needs to be further improved.

Acupuncture, as a traditional Chinese medicine therapy, is a kind of nerve stimulation technology. In clinical practice, it can produce percutaneous tibial posterior stimulation and sacral nerve regulation through acupuncture and moxibustion treatment, forming electrical nerve effect so as to play a therapeutic role. At present, acupuncture has been widely used in the treatment of nocturia. An increasing number of clinical studies have shown that acupuncture can reduce the number of nocturia and nocturnal urine volume, and help improve patients’ bladder function and lower urinary tract symptoms. Acupuncture, as a traditional Chinese medicine therapy, is a kind of nerve stimulation technology. In clinical practice, it can produce percutaneous tibial posterior stimulation and sacral nerve regulation through acupuncture and moxibustion treatment, forming electrical nerve effect so as to play a therapeutic role. At present, acupuncture has been widely used in the treatment of nocturia. An increasing number of clinical studies have shown that acupuncture can reduce the number of nocturia and nocturnal urine volume, and help improve patients’ bladder function and lower urinary tract symptoms. Although some studies on acupuncture and moxibustion in the treatment of nocturia, the meta-analysis of acupuncture in the treatment of nocturia is relatively limited and there is A lack of efficacy data to the treatment of nocturia still needs to be further improved.

3.2. Inclusion criteria
3.2.1. Type of studies. All RCTs reported will be included without regional and language restrictions. Animal studies, cohort studies, case-controlled studies, case reports, and expert experience will be excluded.

3.2.2. Type of participants. Participants in the study were diagnosed with nocturia. On the basis of International Continence Society -2002 report on standardization of terminology in nocturia “the complaint that the individual has to wake at night 1 or more times to void” regardless the age, gender, race, country, and nocturia type.

3.2.3. Type of interventions. The purpose of this study is to observe the clinical study of acupuncture in the treatment of nocturia. Acupuncture treatment were used in the experiment, including body acupuncture, warm acupuncture, electro-acupuncture, auricular acupuncture, fire needling, elongated needle, moxibustion, or herbs-partitioned moxibustion.

3.2.4. Type of comparators. The control group that will include nonacupuncture techniques, such as behavioral therapy, sham acupuncture, placebo, or pharmacotherapy. The acupoint numbers, retaining time, and frequency will not be restricted in this protocol.

3.2.5. Type of outcome measures
3.2.5.1. Primary outcomes. The primary outcome measures will be total and frequency of nocturnal urination.

3.2.5.2. Secondary outcomes. Secondary outcomes will include the ratio of nocturnal urine volume to daytime urine volume. Urine/blood osmotic pressure ratio, urine specific gravity value. change in N-QoL, Pittsburgh Sleep Quality Index Scale, as well as a standard battery of blood and urine analyses, vital signs, and physical examinations.

3.3. Exclusion criteria
- Non-RCTs;
- None of the valid outcome indicators;
- Duplicated data;
- Invalid outcome indexes.

3.4. Search methods for identification of studies
3.4.1. Electronic searches. RCTs of acupuncture for nocturia will be searched in the relevant database, including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure Wanfang Database, Chinese Biomedical Literature Database, and Chinese Scientific Journal Database. The key words include “acupuncture,” “nocturia,” “complementary

| Search strategy used in PubMed database. |
|------------------------------------------|
| **Order** | **Search items** |
| #1 | (Nocturia[MeSH Terms]) AND (Nocturia) |
| #2 | ((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((Acupuncture[MeSH Terms]) OR (Pharmacopuncture)) OR (Acupuncture therapy) OR (Electroacupuncture) OR (Manual acupuncture) OR (Dry Needle)) OR (Moxibustion[MeSH Terms]) OR (moxibustion)) OR (Acupuncture, Ear[MeSH Terms]) OR (Acupuncture, ear) OR (Ear acupuncture) OR (Auricular acupuncture) OR (Ear acupuncture) OR (Acupuncture, auricular) OR (Acupuncture, auricular) OR (Auricular acupuncture) OR (Warm acupuncture) OR (Elongated needle)) |
| #3 | Randomized controlled trial[Publication Type] OR Randomized[Title/Abstract] OR placebo[Title/Abstract] |
| #4 | #1 AND #2 AND #3 |

2
therapy,” “randomized controlled trial,” “randomized controlled trial” and “systematic review.” An equivalent translation of the same search terms will be used to search in the Chinese databases. The search strategy of PubMed is shown in Table 1.

3.4.2. Searching other resources. A review or meta-analysis of relevant RCT systems will be conducted via electronic search. We will also manually search the references of relevant articles that is not included in the electronic database to further identify eligible studies.

3.5. Selection of studies

The studies of electronic searches will be exported to EndNote V.9.1 software. Two authors will independently undertake the process of selecting the search results according to the inclusion and exclusion criteria. They will review and screen the titles and abstracts retrieved by literature search to exclude irrelevant trials. The causes of both selections will be documented and full texts will be obtained and checked for further evaluation if necessary. When there is uncertainty about eligibility of the study, reviewers will arrive at a decision by via discussion and consensus with a third reviewer. The selection process will be showed in a PRISMA flow diagram (Fig. 1).

3.6. Data extraction and management

Data will be extracted independently from the selected articles by 2 reviewers using a Microsoft Excel spreadsheet. They will review and screen the titles and abstracts retrieved by literature search to exclude irrelevant trials and cross-check. If there is any disagreement, discuss and resolve it and consult the third party for assistance in judgment. Data extraction including:

1. author, year, random method, sample size, age;
2. specific details of the intervention, treatment, amount of treatment, duration of intervention, acupoint selection, and course of treatment;
3. outcome indicators and outcome measurement data of concern.

Disagreements between reviewers in the process of data extraction were resolved by discussing with a third reviewer. Incomplete data will be provided by contacting corresponding authors.

3.7. Assessment of the methodological quality

The risk of deviation was assessed by 2 reviewers against criteria provided in the Cochrane Intervention Systematic Evaluation Manual.[33] It includes the following 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, Any disagreement should be solved in consultation with a third reviewer.

3.8. Measures of treatment effect

Weighted mean difference or standardized mean difference will be adopted as statistical indicators in the analysis of continuous outcomes and the relative risk will be used to assess the treatment effect for dichotomous outcomes. 95% of the confidence intervals will be determined in pooled estimates.

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

Statistical heterogeneity should be evaluated by Chi-Squared tests and $I^2$ statistic. The results of the $I^2$ statistic, which determine the use of fixed-effects model or random-effects model, cover unimportant heterogeneity (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%), and considerable heterogeneity (75%–100%). A random-effect model or subgroup analysis should be used when there exists significant heterogeneity.

3.11. Data synthesis

We will run meta-analyses using the Review Manager (RevMan) V.5.3 software. If the result of heterogeneity in $I^2 < 40\%$, the fixed-effects model will be used for data synthesis and analysis; If $I^2 \geq 40\%$ and $< 75\%$, the random-effects model will be implied; If $I^2 \geq 75\%$, it means there is considerable heterogeneity between studies. Alternatively, we will eliminate low-quality research and use sensitivity analysis to investigate which studies will be the most likely have a significant effect on heterogeneity. If synthesize quantitatively is not possible, we’re going to do a qualitative description.

3.12. Subgroup analysis

If there is significant heterogeneity in the results, we will conduct a subgroup analysis to investigate differences in age, gender, length of disease duration, outcome style, etc.

3.12.1. Sensitivity analysis. We will perform sensitivity analyses to verify robustness of results. It includes the impact of methodological quality, study design, and sample size.

3.13. Grading the quality of evidence

Two reviewers will independently use the Grading of Recommendations Assessment, Development and Evaluation, scored each criterion as having high risk, low risk or unclear risk.

3.14. Ethics and dissemination

The study will be published in peer-reviewed journals or relevant conferences. Ethical approval is not required. The results of this study will provide potential guidance for promoting the treatment strategy of nocturia patients.

4. Discussion

The frequent nocturnal urination caused by nocturia can negatively affect patients’ sleep quality, mental state, and N-QoL.[34] Many beneficial explorations on nocturia have been made around the world, which have made many important contributions to the understanding of etiology and pathology of nocturia as well as the prevention and treatment of the disease, and provided a variety of options for improving the N-QoL of patients with nocturia. However, due to the characteristics of
recurrent nocturia and lingering difficulty in healing, the current treatment is difficult to achieve long-term good control of the symptoms of patients, and the safety of its prognosis and efficacy is still not ideal. Therefore, there is an urgent need for a stable, safe, and convenient treatment. Therefore, there is an urgent need for a stable, safe and convenient treatment. Acupuncture, as a traditional Chinese medicine therapy, is also increasingly widely used in the treatment of nocturia. Several RCT studies recently have also provided relevant evidence to estimate the effectiveness of acupuncture for treating patients with nocturia. But now is still lack of enough according to support to get a clear conclusion, therefore this study for the first time to a systematic review and meta-analysis of available literature, objectively evaluate the clinical efficacy of acupuncture in the treatment of nocturia, acupuncture treatment for the future nocturia provide objective statistics, and for clinicians treating nocturia increased reliable reference, benefit the patients.

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For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

Figure 1. Flowchart of literature selection.
Author contributions

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