

Jingui Shenqi pill for nocturia due to nocturnal polyuria

A protocol for systematic review and meta-analysis

Zhipeng Fan, MM, Zhaodi Wang, MM, Jiashuai Deng, MM, Yong Jiang, MD*

Abstract

Background: The incidence of nocturia is high and will seriously affect patients' physical and mental health. Nocturnal polyuria is the most critical cause of nocturia, There are few drugs currently used to treat nocturia due to Nocturnal Polyuria (NP). The guide highly recommends only Desmopressin. There is an urgent need to find new drugs. Jingui Shenqi pill (JSP) is a Chinese patent medicine, it is widely used in China to treat NP. However, there is no evidence-based medical evidence to prove its safety and effectiveness. The purpose of this systematic review is to evaluate the efficacy and safety of JSP in the treatment of NP.

Methods: We will search the randomized controlled trials (RCTs) including JSP for NP and published from the inception of the database to Oct 2020 by the following eight databases: Embase, Cochrane Library, PubMed, MEDLINE, the China National Knowledge Infrastructure, Cqvip Database, and Wanfang Data, the Chinese Biomedical Literature Database. There is no language and publication status restriction. The primary outcomes will include Nocturnal urine volume, the number of nocturnal voids, Nocturnal polyuria index (Nocturnal total urine volume /24 h total urine volume). We will perform the data synthesis, sensitivity analysis, subgroup analysis, and bias assessment risk using RevMan V.5.3. The reporting bias will be assessed using a funnel plot and Egger test.

Results: This study may provide additional evidence of JSP for NP in the effectiveness and safety and alternative therapy for NP.

Conclusions: In this systematic review, we will assess whether JSP is an effective and safe medicine for nocturia.

Abbreviations: CI = confidence interval, JSP = Jingui Shenqi pill, MD = mean difference, NP = nocturia due to nocturnal polyuria, OR = odds ratio, RCTs = randomized controlled trials, TCM = traditional Chinese medicine.

Keywords: Jingui Shenqi pill, effectiveness, safety, nocturia, nocturnal polyuria, systematic review

1. Introduction

Nocturia is defined as the patient must wake up one or more times to void at night.^[1] It is generally believed that being awake at night to void two or more times has clinical significance and will severely impact patients' quality of life.^[2,3] Nocturia is very common, and the incidence of nocturia is high among adults, especially the elderly. Studies have reported that the prevalence of clinically relevant nocturia (≥ 2 voids per night) in young men

aged 20 to 40 years is 2% to 16.6%. The prevalence rate of young women is 4.4% to 18%. The prevalence rate of older men than 70 years is 29% to 59.3%. In older women than 70 years, the incidence of nocturia is 28.3% to 61.5%.^[4] Studies have shown that nocturia can seriously affect patients' health-related quality of life (HRQL). It will increase the risk of depression, cardiovascular and cerebrovascular events, falls and fractures, and mortality.^[5-9]

Nocturia has brought a severe socioeconomic burden. A study showed that only the hospitalization cost for a hip fracture caused by nocturia in the EU in 2014 was €1.0 billion. In the United States, the loss of falls due to nocturia alone amounts to about \$1.5 billion each year.^[10]

The leading causes of nocturia are divided into the following categories: nocturnal polyuria, global polyuria, reduced bladder capacity, sleep disorders, and circadian clock disorders. Christoph Klingler et al have found that nocturnal polyuria is the leading cause of nocturia.^[11]

At present, there are few drugs for NP. According to the guidelines, the only drug highly recommended to treat NP is Desmopressin, which increases the risk of hyponatremia highly recommended.^[12,13] There is a medical need for a new medicine for NP.

JSP is a Chinese patent medicine for NP. It has been clinically used for more than two thousand years. It was first recorded in *the Synopsis of Prescriptions of the Golden Chamber*. It consists of the following herbs: Moutan Cortex (Mu DanPi), Alimria Rhizoma (Ze Xie), Cinnamomi Ramulus (Gui Zhi), Achyranthis

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

Basic Medical College, Chengdu University of TCM, Chengdu, Sichuan Province, China.

* Correspondence: Yong Jiang, Basic Medical College, Chengdu University of TCM, Chengdu 610075, Sichuan Province, China (e-mail: jiangyong@pyztc.com).

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Bidentatae Radix (Niu Xi), Rehmanniae Radix (Di Huang), Dioscoreae Rhizoma (Shan Yao), Poria (Fu Ling), Corni Fructus (Shan Zhu Yu), Plantaginis Semen (Che Qian Zi), and Aconiti Lateralis Radix Praeparata (Fu Zi).^[14] Many modern studies have shown that it is effective in treating NP.^[15-19] but due to the small sample size, it is challenging to get reliable conclusions. This study aims to provide evidence-based medical evidence for clinical use of JSP as an alternative therapy for NP by identifying and critically evaluating Randomized Controlled Trials (RCTs) of JSP for treating NP.

2. Methods

2.1. Study registration

The protocol for this systematic review was registered on INPLASY (10.37766/inplasy2020.11.0048) and is available in full on the inplasy.com (<https://doi.org/10.37766/inplasy2020.11.0048>).

The protocol will be strictly implemented under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA-P).

2.2. Ethics and dissemination

Ethical approval is not required as we need not collect primary data. The final results of the study will be published in a peer-reviewed journal.

2.3. Eligibility criteria

2.3.1. Types of studies. All RCTs about JSP for NP will be included regardless of language. The following studies will be excluded: animal experiments, case series, quasi-RCTs, cell experiments, Case reports, non-RCTs.

2.3.2. Participants. Patients diagnosed with NP and aged > 18 years old will be included, regardless of gender, economic status, or restrictions.

2.3.3. Types of interventions. The intervention group used only JSP or combined JSP with another active treatment, pharmacological or non-pharmacological. The control group used another active treatment or placebo or no treatment. The dosage and frequency will not be restricted.

2.3.4. Types of outcome measures. The primary outcomes include Nocturnal urine volume, the number of nocturnal voids, Nocturnal polyuria index (Nocturnal total urine volume /24h total urine volume). Secondary outcomes include the time to first void, 24 hours total urine volume, 24 hours total number of voiding

2.4. Exclusion criteria

We will exclude the following studies: studies where complete data are not available; studies with data errors; studies using wrong intervention methods or random methods. For duplicate documents, we will select only one of them.

2.5. Search strategy

The following eight electronic databases, including PubMed, Cochrane Library, EMBASE, MEDLINE, the China National Knowledge Infrastructure, the Chinese Biomedical Literature

Database, Cqvip Database, and Wanfang Data, will be comprehensively searched. All the documents retrieved are from the time of establishing the database to Oct 10, 2020. We will use the following terms to search. "nocturia," "nycturia," "noctur," "nocturnal polyuria," "nocturnal urine production," "nocturnal urine volume," "Jinkui Shenqi pill," "randomized clinical trials," and "RCTs." To identify additional references, we will manually search the reference lists of primary studies and related reviews. We also will search the following resources to identify ongoing or completed clinical trials: Google scholar, OpenGrey, Chinese Clinical Trial Registry, ClinicalTrials.gov, International Clinical Trials Registry Platform.

2.6. Study selection and data extraction

2.6.1. Study selection. We will use EndNote X7 to manage literature and remove duplications. The two reviewers will individually screen out potential eligible studies based on the search strategy. The two researchers will carefully read the title and abstract to eliminate irrelevant studies and then read the full text to confirm eligible studies. If any dispute occurs, the dispute will be resolved through consensus or consultation with the third reviewer. The process will be shown through the PRISMA flow diagram (Fig. 1).^[20]

2.6.2. Data extraction. Data extraction is fulfilled by two researchers independently. Data extracted include

- Literatures information (title, author, year of publication, country);
- Study characteristics (Study design, details of randomization process, sample size, inclusion and exclusion criteria);
- Participant characteristics (gender, age, diagnosis criteria);
- Intervention details;
- Outcomes.

Any disputes about data extraction will be resolved through consensus. If necessary, the study's further details or clarification will be supplemented by contacting the original author.

2.7. Assessment of risk of bias

Two reviewers will use the Cochrane Collaboration's tool to assess methodological quality.^[21] We will evaluate the following seven aspects. Including random, blinding of participants and investigators, sequence generation, the blindness of outcome assessments, allocation concealment, selective outcome reporting, incomplete outcome data, and other biases. Each included study will be assessed as low, unclear, or high bias based on the results. Any discrepancies will be resolved by further discussing it with a third reviewer.

2.8. Statistical analysis

For data analysis, we will use RevMan 5.3.0 provided by the Cochrane Collaboration. The chi-square test and I^2 statistic will be used to assess the heterogeneity of similar studies. If $P \geq .05$ and $I^2 \leq 50\%$, it is low heterogeneity. As a result, a fixed-effects model will be used. If $P < .05$ and $I^2 > 50\%$, there will be heterogeneity. A random-effects model will be used. We will use an odds ratio (OR) with a 95% confidence interval (CI) to represent the enumeration data. We will express the measurement data by the mean difference (MD with 95% CI). A statistically significant difference is considered to be $P < .05$.

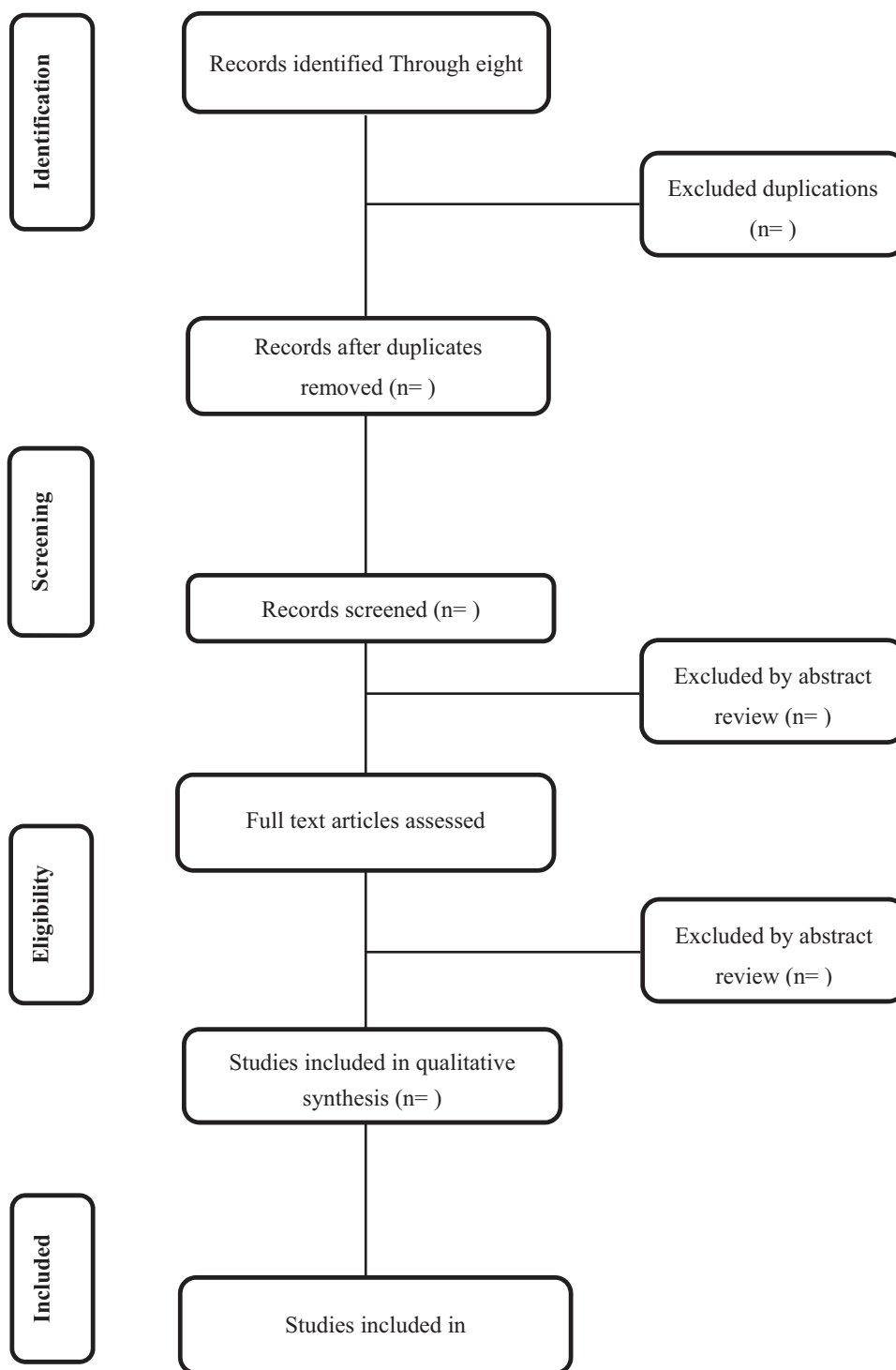


Figure 1. Flow diagram of the study selection process.

2.9. Subgroup analysis and sensitivity analysis

To seek the potential source of heterogeneity, subgroup analysis, and sensitivity analysis will be performed based on various study characteristics such as study quality, location of study, publication date, trial publishing status, type of comparisons, history of pulmonary diseases, duration of treatment, frequency of delivery, age, gender.

2.10. Publication bias

We evaluate if there will is a reporting bias using a funnel plot and the Egger test.

3. Discussion

TCM believes that the deficiency of kidney yang causes NP. JSP is a standard medicine used in TCM to treat deficiency of kidney

yang. Modern research has found that it can treat NP.^[15,16] Because of the remarkable effect, JSP is now widely using to treat NP in China. We hope to obtain an evidence-based medicine that JSP is a safe and effective drug for NP treatment by systematically evaluating the RCTs of NP's treatment using JSP

Author contributions

Conceptualization: Zhipeng Fan, Zhaodi Wang, Jiashuai Deng.

Data curation: Yong Jiang.

Investigation: Zhaodi Wang.

Methodology: Zhipeng Fan, Zhaodi Wang.

Project administration: Zhipeng Fan, Jiashuai Deng.

Software: Yong Jiang.

Supervision: Jiashuai Deng.

Validation: Zhaodi Wang.

Writing – original draft: Zhipeng Fan.

Writing – review & editing: Zhipeng Fan, Zhaodi Wang.

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