BMJ Open

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007009
Article Type:	Protocol
Date Submitted by the Author:	24-Oct-2014
Complete List of Authors:	Zhang, Wei; China Academy of Chinese Medical Sciences, Guang'anmen Hospital, Department of Acupuncture Yu, Jinna; China Academy of Chinese Medical Sciences Guang'anmen Hospital, Department of Acupuncture LIU, Zhishun; Guang'anmen hospital, China Academy of Chinese Medical Sciences, Department of acupuncture PENG, Weina; Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Department of acupuncture
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Urology
Keywords:	COMPLEMENTARY MEDICINE, Adult urology < UROLOGY, Prostate disease < UROLOGY

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Wei Zhang, Jinna Yu, Zhishun Liu , Weina Peng

Title page

Corresponding author: Dr. Wei Zhang

Department of Acupuncture , China Academy of Chinese Medical Sciences Guang'anmen Hospital, Beijing, China

Address: No.5 Bei Xian Ge Street, Xuan Wu District , Beijing 100053

e-mail: zhangwei_7108@126.com

Telephone: 008613522728826

Jinna Yu

Department of Acupuncture , China Academy of Chinese Medical Sciences Guang'anmen Hospital, Beijing, China

Zhishun Liu

Department of Acupuncture , China Academy of Chinese Medical Sciences Guang'anmen Hospital, Beijing, China

Weina Peng

Department of Acupuncture , China Academy of Chinese Medical Sciences Guang'anmen Hospital, Beijing, China

Key words: acupuncture; benign prostatic hyperplasia; traditional Chinese medicine; systematic review

Word count 1830

ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered among aged men. BPH has been treated with acupuncture inside and outside China; however, its effects were uncertain. This review aims to assess the efficacy and safety of acupuncture therapy for BPH.

Methods and analysis: Six databases will be searched from their inceptions: the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library; MEDLINE; EMBASE; Chinese Biomedical Database; the China National Knowledge Infrastructure (CNKI); the VIP Database (VIP), and Wanfang Database. Randomised controlled clinical trials (RCTs) with acupuncture for BPH will be included. Outcome measures include urologic symptom scores, urodynamic measures, quality of life scales; et al. Adverse effects will be assesses and reported for safety evaluation purpose. Study selection and data extraction will be performed by two independent reviewers. Quality assessment (assessment of risk of bias) and data synthesis will be implemented using Review Manager (RevMan) software (ver 5.2.3).

Dissemination: The protocol and full version of this systematic review will be published in a peer-reviewed journal. Updates will be conducted if there is enough new evidence that may cause any change of review conclusions.

Trial registration number: PROSPERO 2014:CRD42014013645.

Strengths and limitations of this study

This review may provide more options to patients, clinicians and policy makers concerning intervention of BPH.

Databases will be searched and trials will be screened without restriction of languages. Trials published in languages except Chinese and English will be translated by qualified translators only if they are potentially included by judging their titles and abstracts in English.

The trial screening, data extraction and risk of bias assessment of this review will be conducted by two reviewers independently.

Highly individualized treatment has always been characteristic of acupuncture therapy, including variation of treatment frequency, stimulation methods and courses of treatment. This may make it difficult to do data synthesis because of the clinical heterogeneity.

INTRODUCTION

Description of the condition

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered among aged men. Histological investigations have shown that more than 40% of men in their fifties and nearly 90% of men in their eighties suffer from BPH.[1] Lower urinary tract symptoms (LUTS) associated with BPH include obstructive symptoms (weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling, abdominal straining), and irritative symptoms (urinary frequency, urgency and nocturia).[2,3]In the United States treatment of BPH accounts for approximately 4.5 million physician-office visits [4]and results in more than 300,000 prostatectomies annually.[5] In China, prostate specimens from 321 deceased were collected from 1989 to 1992. The frequency of BPH was 13.2% among those 41 to 50 years old and increased until it reached 83.3% among those 81 to 90 years old. The histologic frequency of BPH in China was similar to that in Western countries.[6] Treatment of BPH includes minimally invasive therapy (MIT), surgery and medical therapy. The pharmacologic use of plants and herbs (phytotherapy) was another option for the treatment of BPH and its usage has been growing steadily in some countries.[7, 8]

Description of the intervention

Acupuncture is a very important part of Traditional Chinese Medicine (TCM). It has a literary history of more than 2000 years.[9]Acupuncture is a therapy that inserts needles into certain points, called "Xue Wei," of the human body. Many centuries ago acupuncture developed into a discipline, with its own theory and practice. It is believed in TCM theory that acupuncture can strengthen the human body's vital essence, called "Qi," and can remove the blockage of channels. Both a World Health Organization report and a National Institutes of Health consensus conference provided lists of conditions that would be potentially treated with acupuncture. [10.11]

How the intervention might work

Acupuncture is also helpful with a wide range of other diseases. In China, BPH has been treated with acupuncture, and the procedure's efficacy has been tested by some research. In an animal model it has been reported that acupuncture can neutralize pathological changes in low levels of nitric oxide synthase (NOS), as well as impaired kidney function, as manifested by high blood urea nitrogen (BUN) and serum creatinine (Cr).[12] Currently, researchers outside China are treating LUTS with acupuncture. Using the International Prostate Symptom Score, a randomized controlled trial (RCT) has assessed the effects of acupuncture on LUTS, as well as prostate specific antigen (PSA). It found that acupuncture to the kidney bladder meridian relieves neither LUTS nor affects PSA.[13]

Why it is important to do this review

To date, the clinical application of acupuncture for BPH and its reporting has been anecdotal, and its effects have not been systematically reviewed.

OBJECTIVES

Our objective is to conduct a systematic review, and if possible, a quantitative meta-analysis, with evidence available from randomized controlled trials to assess the efficacy and safety of acupuncture therapy for BPH.

METHODS

The protocol of this systematic review has been registered on PROSPERO 2014 (registration number: CRD42014013645). The methods of this systematic review protocol have been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[14]

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials without any language and publication

status restriction will be included in this systematic review.

Types of participants

Men with symptomatic benign prostatic hyperplasia

Types of interventions

Acupuncture therapy with needle insertion, including body, auricular, scalp, as well as electroacupuncture, will be considered. Also included will be acupuncture combined with other treatments or medications, such as herbals. Excluded will be any stimulation other than a needle, such as acupressure, seed stimulation or surface electrodes (TENS).

The control interventions will include: no intervention, placebo acupuncture, sham acupuncture, pharmacological treatments (herbal medicine or conventional medicine, such as 5-alpha reductase inhibitors and alpha blockers), or any other interventions. Placebo acupuncture refers to a needle attached to the skin surface (not penetrating the skin but at the same acupoints). [15]Sham acupuncture refers to: 1) a needle placed in an area close to but not in an acupuncture point;[16] 2) subliminal skin electrostimulation via electrodes attached to the skin.[17]

Types of outcome measures

The primary outcome measures will be change in urological symptoms as measured by validated urologic symptom scores, including Boyarsky, the American Urologic Association Symptom Score, and the International Prostate Symptom Score (IPSS). Secondary outcome measures will include: 1) Quality of life score (QOL); 2) Adverse events, such as intolerable pain during acupuncture, bleeding during or after the session, breaking or winding of the needle, injury to organs (e.g., pneumothorax), and fainting. The number and severity of adverse events should be recorded; 3) Urodynamic measures, which are defined as change in peak urine flow (meaured in mL/sec), mean

urine flow (measured in mL/sec), residual urine volume (measured in mL), nocturia (measured in times per evening), and changes in prostate size (measured in cc).

Search methods for identification of studies

Electronic searches

We will search the following electronic databases irrespective of language and publication status: the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library; MEDLINE; EMBASE; Chinese Biomedical Database; the China National Knowledge Infrastructure (CNKI); the VIP Database (VIP), and Wanfang Database. The process of study selection is summarized in a PRISMA flow diagram（figure 1）.

Other sources

Non-electronic search will be implemented for further information including a) the reference lists of all identified papers, as well as relevant reports of clinical trials or review articles; b) conference proceedings.

Search strategy

Below is the search strategy for MEDLINE, a Chinese version of the same search items will be used for searching the Chinese databases.

1 randomised controlled trial

#2 controlled clinical trial

#3 randomised

#4 randomized

#5 randomly

#6 trial

#7 or/1-6

#8 benign prostatic hyperplasia or bph/

#9 lower urinary tract symptoms or luts/

#10 or/8-9

#11acupuncture/

#12 acupuncture points/

#13 (electroacupuncture or electro- acupuncture).tw.

#14 electroacupuncture.tw.

#15 acupuncture$.tw.

#16 acupoints.tw.

#17 meridians/

#18 or /11-17

#19 7 and 10 and 18

Data collection and analysis

Selection of studies

Two reviewers, WZ and WP, will independently decide on eligibility of studies. Randomised controlled trials which meet the criteria of good or acceptable rate of dropouts (no more than 20%), withdrawals and lost to follow ups will be included for this review. A third party (ZL) will be involved to resolve any disagreement in case of occurrence.

Data extraction and management

A data extraction form will be developed and study data will be assessed and extracted independently by two reviewers, JY and WP. The following data will be extracted from each included study: patients' demographic characteristics, including maximum, minimum and mean age; inclusion and exclusion criteria; and type, frequency and treatment course of acupuncture therapy and outcomes. Type, severity and number of adverse effects, as well as number and reasons for dropouts, withdrawals, and lost of follow-up will also be recorded. Information not available in the trials will be sought from authors by e-mail or telephone. Extracted data will be reviewed by the principal reviewer (WZ) and discrepancies will be judged by the arbitrator, ZL.

Risk of bias assessment

A tool introduced in Cochrane Handbook for systematic reviews of interventions (V.5.2) will be used to assess a broad category of biases. This tool, available through collaboration's website and Review Manager (RevMan) software, presented five sources of bias in clinical trials and their relevant domains which were read a) selection bias: random sequence generation and allocation concealment; b) performance bias: blinding of participants and personnel; c) detection bias: blinding of outcome assessment; d) attrition bias: incomplete outcome data; e) reporting bias: selective outcome reporting. Specific feature of included studies will be judged in each entry of a "risk of bias" table, where the risk of bias will be addressed as low risk, high risk and unclear risk.[18]

Measures of treatment effect

For dichotomous data, risk ratio (RR) with corresponding 95% CIs will be used while continuous data will be expressed as mean differences with 95% CIs. Weighted mean differences will be used for data measured on the same scales and for which the same units are used; otherwise, standardised mean differences will be used.

Dealing with missing data

Reviewers will try to obtain necessary information by contacting the first or corresponding authors of included trials in case of missing data exist through phone, e-mail or post.

Assessment of heterogeneity

We will test for statistical heterogeneity between trial results using a standard chi-squared test and I-squared test to make sure that they are appropriate to be combined.

Assessment of reporting biases

Potential reporting biases will be investigated using the funnel plot. We will use a linear regression approach to measure funnel plot asymmetry on the logarithm scale of the relative risk (RR).

Data synthesis

A meta-analysis will be implemented with the Cochrane Collaboration Review Manager (RevMan 5.2.3) software. All the primary and secondary outcome measures will be combined and analyzed for evidence of homogeneity (P>0.1) using a fixed-effects model. Dichotomous results will be expressed as relative risk (RR) and ratio of risk of the treatment group versus the control group, with 95% confidence intervals (CI). For continuous variables, weighted mean differences (WMD)--the difference between treatment and control pooled means at endpoint--along with their 95% confidence intervals, will be calculated. A random-effects model will be used in case heterogeneity exists.

Sensitivity Analyses

We will implement a sensitivity analyses in order to explore the influence of the following factors on effect size: a) exclude unpublished studies (if there are any); b) analyze study quality; c) exclude any trials with long study duration or are too large to establish how much they dominate the results; d) exclude trials using the following filters: diagnostic criteria, language of publication and race.

Subgroup Analyses

Here we will compare the effects between subgroups by a) different acupuncture types; b) other comparisons; c) location

DISCUSSION

Until now, there is no systematic reviews have examined the use of acupuncture in the treatment of BPH. This review aims to analyze the latest status of acupuncture for benign prostatic hyperplasia. In recent years, randomised controlled studies with higher methodological qualities has been published and the number of trials also increased. [19,20] The process of this review will provide comprehensive and latest summary of evidence on acupuncture efficacious effects for BPH, which will benefit practitioners, patients and policy-makers regarding the use of this ancient therapy in treating BPH.

REFERENCES

1 Berry SL, Coffey, DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; 132:474-9.

2 Christensen MM, Bruskewitz RC. Clinical manifestations of benign prostatic hyperplasia and the indications for therapeutic intervention. *Urol Clin North Am* 1990;17:509-16.

3 Caine M, Schuger L. *The "capsule" in benign prostatic hypertrophy*. NIH Publication No. 87-2881 1987.

4 Wei JT, Calhoun EA, Jacobsen SJ. Chapter 2, *Benign Prostatic Hyperplasia*. In: Litwin MS, Saigal CS, editors(s). Urologic Diseases in America. Washington, DC: US Government Publishing Office, 2007:45-69.

5 McConnell JD, Barry MJ, Bruskewitz RC. *Benign prostatic hyperplasia: Diagnosis and treatment.* Clinical Practice Guideline. No. 8, AHCPR Publication No. 94-0582 Edition. Rockville, MD:Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services 1994.

6 Gu FL, Xia TL, Kong XT. Preliminary study of the frequency of benign prostatic hyperplasia and prostatic cancer in China. *Urology*. 1994; 44(5):688-91.

7 Di Silverio F, Flammia GP, Sciarra A, et al. Plant extracts in benign prostatic

hyperplasia. *Minerva Urol Nefrol* 1993;45:143-9.

8 Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996;78(3):325-6.

9 Skrabanek P. Acupuncture and the age of unreason. *Lancet* 1984; 8387:1169-1171.

10 Bonnerman R. *Acupuncture: the World Health Organization view*. World Health Organization, 1979.

11 NIH Consensus Conference. Acupuncture. *JAMA* 1998; 280:1518–24.

12 Xu JF, Yang ZG. How acupuncture influence the NOS activity and renal function of mice with prostatic hyperplasia. *Shang Hai acupuncture Journal* 2002; 21(6):36-37.

13 Johnstone, P. A. Bloom, T. L, Niemtzow, R. C.et al. A prospective, randomized pilot trial of acupuncture of the kidney-bladder distinct meridian for lower urinary tract symptoms. *Journal of Urology.* 2003; 169(3):1037-9.

14 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339:b2535.

15 Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *The Lancet* 1998; 352:364-365.

16 van Tulder MW, Cherkin DC, Berman B, Lao L, Koes BW. Acupuncture for low back pain. *Cochrane Library*, 2000, Issue 4.

17 Swedish Collaberation on Sensory Stimulation in Stroke. Sensory stimulation after stroke: a randomized controlled trial. *Cerebrovasc Dis* 1999; 9 (suppl 1):28.

18 Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S. eds Cochrane handbook for systematic reviews of interventions version 5.1.0(updated March 2011). The Cochrane collaboration, 2011. http:// www.cochrane-handbook.org

19 Li Jing, Han Chonghua, Cheng Xiaohui, et al. Observation on therapeutic effects of elongated needle therapy on dysuria induced by benign prostatic hyperplasia. *Chinese Acupuncture and Moxibustion*. 2008,10:707-709.

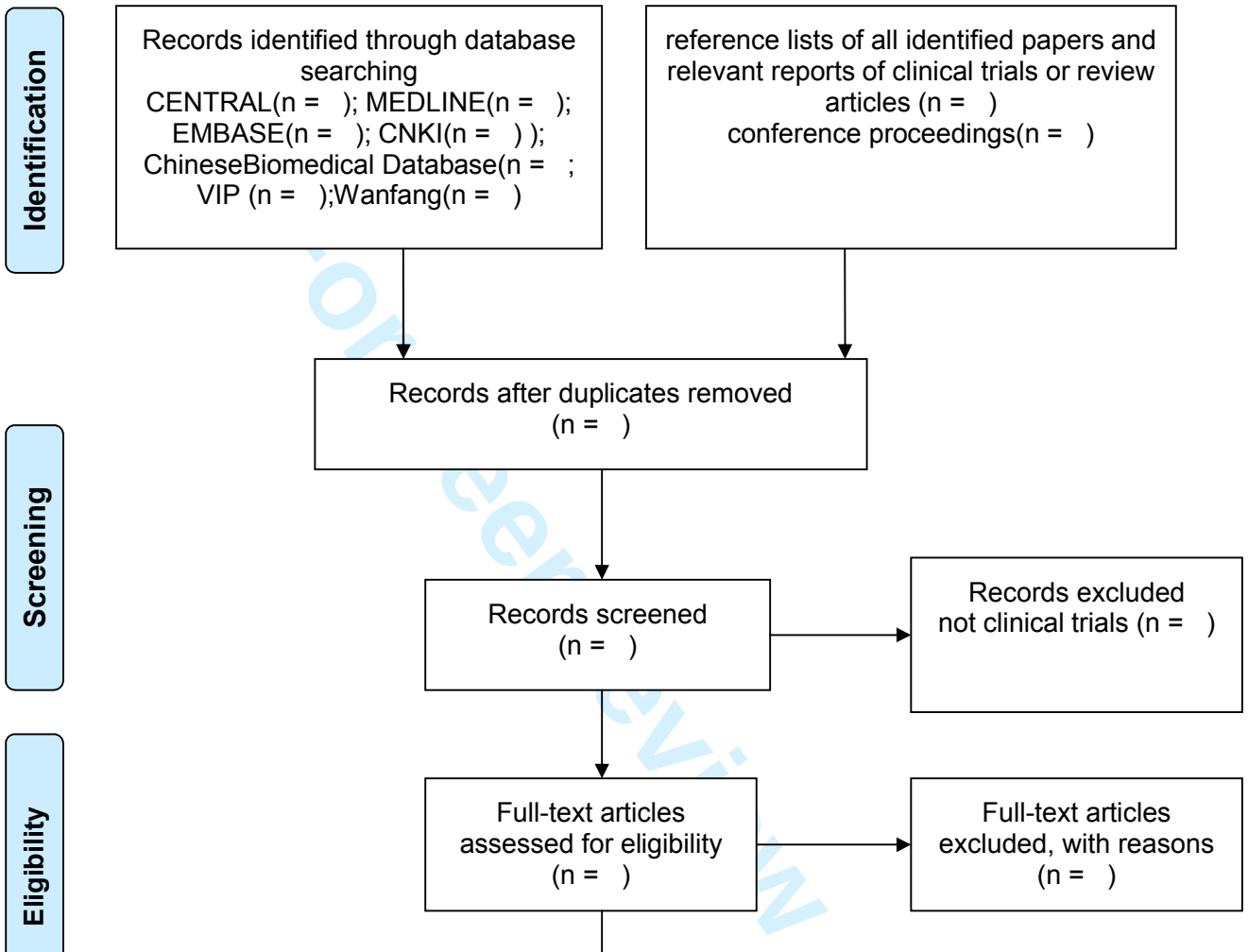
20 Bian Lina, Cheng Yu. Elongated needle combined with scalp needle for benign prostatic hyperplasia-a randomized controlled study. *Journal of Liaoning University of Traditional Chinese Medicine.* 2007, 6:162-163.

Contributors WZ designed and wrote the protocol. WZ will participate in the whole review procedure including data extraction, contacting editors, statistical analysis, quality assessment and completion of the review. ZL checked the protocol and gave comments. WP and JY will extract data and assess quality. In case of disagreement between the two data extractors, ZL will advise on methodology and will work as arbitrator

Funding This work was supported by clinical research fund from China Academy of Chinese Medical Sciences, Guang'anmen Hospital, with a grant number 84382.

Competing interests None.

Figure 1 Flow diagram of the study selection process.



Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	systematic review
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	√
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	√
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	√
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	√
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	√
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	√
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	√
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	√
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	√
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	√
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	√
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	√
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	√

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	√
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	√
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	√
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	√

BMJ Open

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007009.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Feb-2015
Complete List of Authors:	Zhang, Wei; China Academy of Chinese Medical Sciences, Guang'anmen Hospital, Department of Acupuncture Yu, Jinna; China Academy of Chinese Medical Sciences Guang'anmen Hospital, Department of Acupuncture Liu, Zhishun; Guang'anmen hospital, China Academy of Chinese Medical Sciences, Department of acupuncture PENG, Weina; Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Department of acupuncture
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Urology
Keywords:	COMPLEMENTARY MEDICINE, Adult urology < UROLOGY, Prostate disease < UROLOGY

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Wei Zhang, Jinna Yu, Zhishun Liu , Weina Peng

Jinna Yu

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Zhishun Liu

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Weina Peng

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Corresponding author: Dr. Wei Zhang

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Address: No.5 Bei Xian Ge Street, Xuan Wu District, Beijing 100053, China

e-mail:zhangwei_7108@126.com

Telephone: 008613522728826

Key words: acupuncture; benign prostatic hyperplasia; traditional Chinese medicine; systematic review protocol

Word count 2229

ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered in order men. BPH has been treated with acupuncture inside and outside China, but its effects are uncertain. This review aims to assess the efficacy and safety of acupuncture therapy for BPH.

Methods and analysis: Six databases will be searched from their inceptions: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and Wanfang Database. Randomised controlled clinical trials (RCTs) using acupuncture to treat BPH will be included. Outcome measures included urologic symptom scores, urodynamic measures and quality-of-life scales. Adverse events will be assessed and reported for safety evaluation. Study selection and data extraction will be performed by two independent reviewers. Quality assessment (assessment of risk of bias) and data synthesis will be implemented using Review Manager (RevMan) software (ver 5.2.3).

Ethics and dissemination: Ethical approval is not necessary because this systematic review will not include specific patient data. Updates will be conducted if there is enough new evidence that may cause any change in review conclusions.

Trial registration number: PROSPERO 2014:CRD42014013645.

Strengths and limitations of this study

- This review may provide more options to patients, clinicians and policy makers concerning BPH interventions.
- Databases will be searched and trials will be screened without restriction to languages. Trials published in languages other than Chinese and English will be translated by qualified translators if they can be potentially included after reading their English titles and abstracts.
- The trial screening, data extraction and risk of bias assessment of this review will be conducted by two reviewers independently.
- Highly individualized treatment has always been characteristic of acupuncture therapy, including variation of treatment frequency, stimulation methods and courses of treatment. This may make it difficult to perform data synthesis because of clinical heterogeneity.

INTRODUCTION

Description of the condition

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered among older men. One histological investigation from 1984 showed that more than 40% of men in their 50s and nearly 90% of men in their 80s experience BPH.[1] However, different absolute prevalence rates were reported later in multinational population-based studies.[2,3] Lower urinary tract symptoms (LUTS) associated with BPH include obstructive symptoms (weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining), and irritative symptoms (urinary frequency, urgency and nocturia).[4,5]In the United States, treatment for BPH accounted for approximately 4.5 million physician-office visits in 2000[6] and resulted in more than 300,000 prostatectomies in 1994.[7]In China, prostate specimens from 321 deceased patients were collected from 1989 to 1992. The frequency of BPH was 13.2% among those aged 41- 50 years and increased until it reached 83.3% among those aged 81-90 years. This histological frequency of BPH in China was similar to that in Western countries.[8] Treatment for BPH includes minimally invasive therapy (MIT), surgery and medical therapy. The pharmacologic use of plants and herbs (phytotherapy) is another option for the treatment of BPH and its use has been growing steadily in some countries.[9, 10]

Description of the intervention

Acupuncture is a very important part of traditional Chinese medicine (TCM) and it has a literary history of more than 2000 years.[11]Acupuncture is a therapy that inserts needles into certain points on the body called “Xue Wei”. Centuries ago, acupuncture was developed into a discipline with its own theory and practice. TCM theorizes that acupuncture can strengthen the human body’s vital essence, called “Qi”, and remove the blockages in channels.[12]Both a

World Health Organization report and a National Institutes of Health consensus conference provided lists of conditions that could be potentially treated with acupuncture.[13.14]

How the intervention might work

Acupuncture is also helpful for a wide range of other diseases.[15] In China, BPH has been treated with acupuncture and the procedure's efficacy has been tested by some studies. In one animal model it was reported that acupuncture can neutralise pathological changes in low levels of nitric oxide synthase and impaired kidney function, which manifested as high blood urea nitrogen and serum creatinine.[16]

Why it is important to do this review

To date, the clinical application of acupuncture for BPH and its reporting has been anecdotal, and its effects have not been systematically reviewed.

OBJECTIVES

We aim to conduct a systematic review, and if possible, a quantitative meta-analysis, with evidence available from randomized controlled trials into the comparative effectiveness and harms of acupuncture for men with symptomatic BPH compared with various types of control interventions. Outcomes including validated urologic symptom scores, quality-of-life score, urodynamic measures, and prostate size measurements will be included.

METHODS

The protocol of this systematic review has been registered on PROSPERO 2014 (registration number: CRD42014013645). This systematic review protocol has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[17]

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials without any language or publication status

restrictions will be included in this systematic review.

Types of participants

We will include studies investigating men with symptomatic BPH determined by elevated urinary symptom scores including the Boyarsky Score, the American Urologic Association Symptom Score, and the International Prostate Symptom Score (IPSS). There will be no restrictions on other diagnostic methods such as urinary flow rates or ultrasound. Patients with diagnoses of other diseases that may cause urinary tract symptoms such as prostatic cancer and neurogenic bladder will be excluded.

Types of interventions

For the treatment group, acupuncture therapy with needle insertion will be considered, including body acupuncture, auricular acupuncture, scalp acupuncture, and electroacupuncture. We will also include acupuncture combined with other treatments or medications, such as herbs. Excluded interventions will be any stimulation other than that of a needle, such as acupressure, seed stimulation or surface electrodes.

Control interventions will include: no intervention, placebo acupuncture, sham acupuncture, pharmacological treatments (herbal medicine or conventional medicine, such as 5-alpha reductase inhibitors and alpha blockers), surgery or any other interventions. Placebo acupuncture includes treatments that attach a needle to the skin surface (not penetrating the skin but at the same acupoints). [18]Sham acupuncture includes: a needle placed in an area close to but not in an acupuncture point, [19] and subliminal skin electro stimulation via electrodes attached to the skin.[20]

Types of outcome measures

Primary outcome measures will be changes in urological symptoms as measured by validated urologic symptom scores, including the Boyarsky Score,

the American Urologic Association Symptom Score, and IPSS. Secondary outcome measures will include: quality-of-life score; urodynamic measures, which are defined as changes in peak urine flow (measured in mL/s); mean urine flow (measured in mL/s) and residual urine volume (measured in mL); nocturia (measured in times per evening); and changes in prostate size (measured in cc).

Adverse events will be recorded including intolerable pain during acupuncture, bleeding during or after the session, breaking or winding of the needles, injury to organs (e.g., pneumothorax), and fainting. The number and severity of adverse events will be recorded.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases irrespective of language and publication status: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, the Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and the Wanfang Database.

Other sources

A non-electronic search will be implemented for further information including the reference lists of all identified papers, relevant reports of clinical trials or review articles, and conference proceedings.

Search strategy

Below is the search strategy for MEDLINE, a Chinese version of the same search items will be used for searching the Chinese databases.

1 randomised controlled trial

#2 controlled clinical trial

#3 randomised

#4 randomized

#5 randomly

#6 trial

#7 or/1-6

#8 benign prostatic hyperplasia or bph/

#9 lower urinary tract symptoms or luts/

#10 or/8-9

#11acupuncture/

#12 acupuncture points/

#13 (electroacupuncture or electro- acupuncture).tw.

#14 electroacupuncture.tw.

#15 acupuncture$.tw.

#16 acupoints.tw.

#17 meridians/

#18 or /11-17

#19 7 and 10 and 18

Data collection and analysis

Selection of studies

Two reviewers, WZ and WP, will independently determine the eligibility of studies. Randomised controlled trials that have a good or acceptable rate of dropouts (no more than 20%), withdrawals and lost to follow ups will be included. A third party (ZL) will resolve any disagreements. Study selection is summarised in a PRISMA flow diagram（figure 1）

Data extraction and management

A data extraction form will be developed and study data will be assessed and extracted independently by two reviewers, JY and WP. The following data will be extracted from each included study: patients' demographic characteristics, including maximum, minimum, and mean age; inclusion and exclusion criteria;

type, frequency, and treatment course of acupuncture therapy; and all outcomes. Type, severity, number of adverse effects, and number and reasons for dropouts, withdrawals, and patients lost to follow-up will also be recorded. Information not available in the trials will be sought from authors by e-mail, telephone or post. Extracted data will be reviewed by WZ and discrepancies will be judged by the arbitrator, ZL.

Risk of bias assessment

A tool introduced in the Cochrane Handbook for systematic reviews of interventions (V.5.1) will be used to assess a broad category of biases. This tool, available through collaboration's website and Review Manager (RevMan) software, includes five sources of bias in clinical trials and their relevant domains. The sources of bias are: selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; and reporting bias: selective outcome reporting. Specific feature of included studies will be judged by two reviewers independently in each entry of a "risk of bias" table, where the risk of bias will be addressed as low, high or unclear.[21]

Measures of treatment effect

For dichotomous data, relative risk (RR) with corresponding 95% confidence intervals (CIs) will be used while continuous data will be expressed as mean differences with 95% CIs. Weighted mean differences will be used for data measured on the same scales and for which the same units are used. Otherwise, standardised mean differences will be used.

Dealing with missing data

Reviewers will try to obtain necessary information by contacting the first or corresponding authors of included trials through phone, e-mail or post if there

are missing data.

Assessment of heterogeneity

We will test for statistical heterogeneity between trial results using a standard chi-squared test and I-squared test to make sure that they can be combined.

Assessment of reporting biases

Potential reporting biases will be investigated using the funnel plot. We will use a linear regression approach to measure funnel plot asymmetry on the logarithm scale of the RR.

Data synthesis

A meta-analysis will be implemented with the Cochrane Collaboration Review Manager (RevMan 5.2.3) software. All the primary and secondary outcome measures will be combined and analysed for evidence of homogeneity (P>0.1) using a fixed-effects model. Dichotomous results will be expressed as RR and ratio of risk of the treatment group versus the control group, with 95% CIs. For continuous variables, weighted mean differences (WMD), the difference between treatment and control pooled means at endpoints, and their 95% CIs, will be calculated. A random-effects model will be used if there is statistical heterogeneity.

A narrative synthesis will be provided, if the meta-analysis can not be performed for all or some of expected data from included studies. Text and tables will be used to summarise and explain findings concerning efficacy and safety of acupuncture both within and between studies with reference to participants, interventions, comparators, and outcomes.

Sensitivity analyses

We will implement a sensitivity analyses to explore the impacts of methodological quality and sample size on the robustness of review

conclusions. Meta-analyses will be repeated after excluding studies with lower methodological quality and studies with sample sizes much bigger than those of other studies. Sensitivity analyses will be reported with a summary table and review conclusions will be interpreted with concerns for comparisons between the two meta-analyses.

Subgroup analyses

We will compare the effects between subgroups by: different acupuncture types, including electroacupuncture, elongated needle, and fire needle; different control interventions, such as herbal medicine, Western medicine and phytotherapy; and study locations.

Confidence in cumulative evidence

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology across the domains of risk of bias, consistency, directness, precision and publication bias. [22]Quality of evidence will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect).

DISCUSSION

There are no systematic reviews that have examined the use of acupuncture in BPH treatment. This review aims to analyse the effects of acupuncture on BPH. In recent years, randomised controlled trials with higher methodological qualities investigating acupuncture in BPH treatment have been published.

[23,24]This review will provide comprehensive and current evidence on the therapeutic effects of acupuncture on BPH, which will benefit practitioners, patients, and policy-makers.

Amendments We will provide the date of each amendment describe the change and give the rationale in case we need to amend this protocol.

Contributors WZ is the guarantor**.** WZ and ZL contributed to the conception of this review. WZ drafted the manuscript of protocol and ZL revised it. ZL and WZ developed the search strategies while WP and JY will implement them. WP and JY will also screen the potential studies, extract data and assess quality. In case of disagreement between the two data extractors, ZL will advise on methodology and will work as arbitrator. WZ will complete data synthesis. All authors approved the final version for the publication.

Funding This work was funded by Clinical Research Fund from China Academy of Chinese Medical Sciences, Guang'anmen Hospital, with a funding reference number 84382. This fund covers the expenses including using databases, papers printing, communication and English editing. However, it will not be involved in other aspects of the review such as the design of the protocol and analysis plan.

Acknowledgements: This protocol was edited by Edanz Editing China, an editing company in Beijing for language polishing.

Competing interests None.

REFERENCES

1 Berry SL, Coffey, DS, Walsh PC, *et al*. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; 132:474-79.

2 Meigs JB, Mohr B, Barry MJ, *et al*. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J Clin Epidemiol* 2001; 54:935-44.

3 Platz EA, Smit E, Curhan GC, *et al*. Prevalence of and racial/ethnic variation in lower urinary tract symptoms and noncancer prostate surgery in US men. *Urology* 2002;59:877-83.

4 Christensen MM, Bruskewitz RC. Clinical manifestations of benign prostatic hyperplasia and the indications for therapeutic intervention. *Urol Clin North Am* 1990;17:509-16.

5 Caine M, Schuger L. The "capsule" in benign prostatic hypertrophy. NIH Publication No. 87-2881.Rockville, MD:US Department of Health and Human Services, 1987:221.

6 Wei JT, Calhoun EA, Jacobsen SJ. Chapter 2, Benign prostatic hyperplasia. In: Litwin MS, Saigal CS, eds. Urologic Diseases in America. Washington, DC: US Government Publishing Office, 2007:45-69.

7 McConnell JD, Barry MJ, Bruskewitz RC. Benign prostatic hyperplasia: diagnosis and treatment. Clinical Practice Guideline. No. 8, AHCPR Publication No. 94-0582 Edition. Rockville, MD:, US Department of Health and Human Services 1994.

8 Gu FL, Xia TL, Kong XT. Preliminary study of the frequency of benign prostatic hyperplasia and prostatic cancer in China. *Urology* 1994; 44:688-91.

9 Bales G, Christiano AP, Kirsh E,*et al*. Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Chicago. *Urology* 1999;54:86-89.

10 Barnes PM, Powell-Griner E, McFann K, et al. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data*

2004;27:1-19.

11 Huang LX. Illustrated history on Chinese acupuncture-moxibustion [In Chinese]. Qingdao,China: Qingdao publisher, 2003:186.

12 The Yellow Emperor's Classic for Internal Medicine-Ling Shu [In Chinese]. Beijing, China: People's Health Press, 1963:28.

13 Bonnerman R. Acupuncture: the World Health Organization view. Geneva, Switzerland. World Health Organization,1979.

14 NIH Consensus Conference. Acupuncture. *JAMA* 1998; 280:1518–24.

15 Xiong J. Development History and status of modern medical conditions treated by acupuncture. *Liaoning Journal of Traditional Chinese Medicine* 2009; 36:2155-57.

16 Xu JF, Yang ZG. How acupuncture influence the NOS activity and renal function of mice with prostatic hyperplasia. *Shang Hai acupuncture Journal* 2002; 21(6):36-37.

17 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339:b2535.

18 Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *The Lancet* 1998; 352:364-365.

19 van Tulder MW, Cherkin DC, Berman B, *et al*. Acupuncture for low back pain. *Cochrane Library*, 2000, Issue 4.

20 Swedish Collaberation on Sensory Stimulation in Stroke. Sensory stimulation after stroke: a randomized controlled trial [supplement]. *Cerebrovasc Dis* 1999; 9 :28.

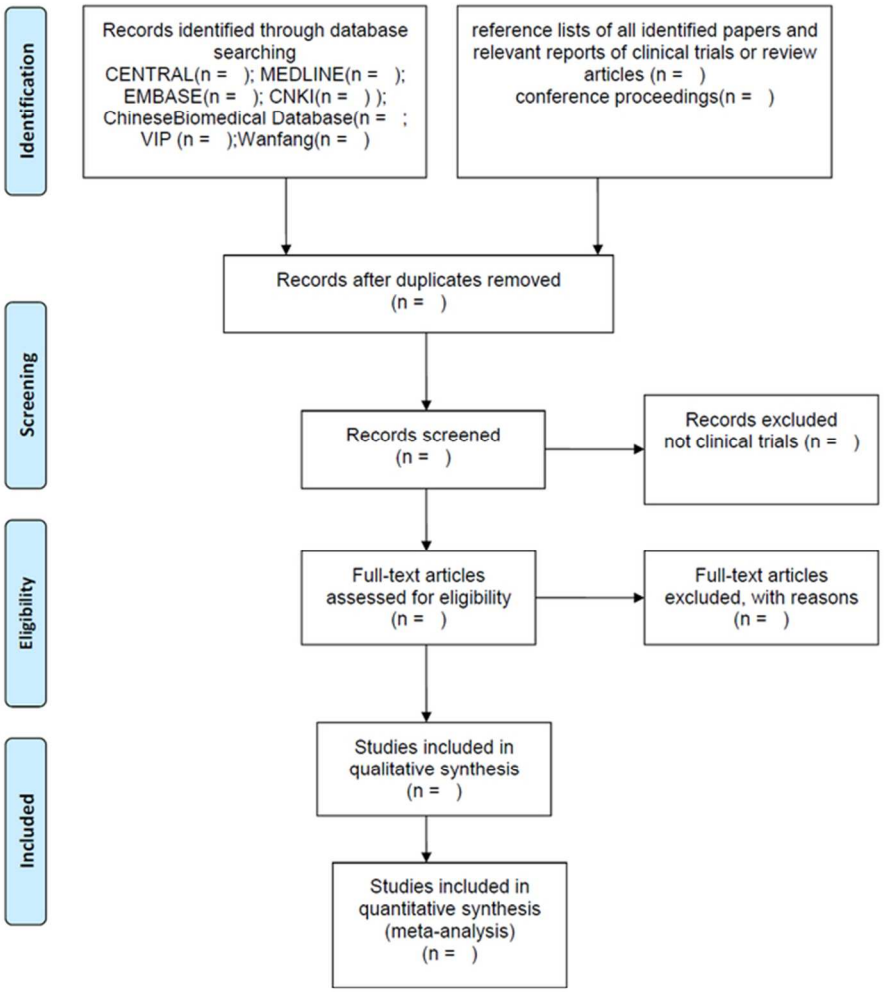
21 Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S. eds Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0(updated March 2011). The Cochrane Collaboration, 2011. http:// www.cochrane-handbook.org (accessed Oct 2014)

22 Balshem H , Helfanda M , Schunemann HJ , *et al.* GRADE Guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol,* 2011, 64: 401-06.

23 Li J, Han CH, Cheng XH, *et al*. Observation on therapeutic effects of elongated needle therapy on dysuria induced by benign prostatic hyperplasia. *Chinese Acupuncture and Moxibustion*. 2008; 10:707-09.

24 Bian L, Cheng Y. Elongated needle combined with scalp needle for benign prostatic hyperplasia-a randomized controlled study. *Journal of Liaoning University of Traditional Chinese Medicine.* 2007;6:162-63.

Figure 1 Flow diagram of the study selection process.



62x76mm (300 x 300 DPI)

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist

Section and topic	Item No	Checklist item	Reported on page#
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	14
Sponsor	5b	Provide name for the review funder and/or sponsor	14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	14
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions,	5

Section and topic	Item No	Checklist item	Reported on page#
		comparators, and outcomes (PICO)	
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or	9

Section and topic	Item No	Checklist item	Reported on page#
		study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10, 11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007009.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Mar-2015
Complete List of Authors:	Zhang, Wei; China Academy of Chinese Medical Sciences, Guang'anmen Hospital, Department of Acupuncture Yu, Jinna; China Academy of Chinese Medical Sciences Guang'anmen Hospital, Department of Acupuncture Liu, Zhishun; Guang'anmen hospital, China Academy of Chinese Medical Sciences, Department of acupuncture PENG, Weina; Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Department of acupuncture
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice, Urology
Keywords:	COMPLEMENTARY MEDICINE, Adult urology < UROLOGY, Prostate disease < UROLOGY

Acupuncture for benign prostatic hyperplasia: a systematic review protocol

Wei Zhang, Jinna Yu, Zhishun Liu , Weina Peng

Jinna Yu

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Zhishun Liu

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Weina Peng

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Corresponding author: Dr. Wei Zhang

Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Address: No.5 Bei Xian Ge Street, Xuan Wu District, Beijing 100053, China

e-mail:zhangwei_7108@126.com

Telephone: 008613522728826

Key words: acupuncture; benign prostatic hyperplasia; traditional Chinese medicine; systematic review protocol

Word count 2403

ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered in older men. BPH has been treated with acupuncture inside and outside China, but its effects are uncertain. This review aims to assess the efficacy and safety of acupuncture therapy for BPH.

Methods and analysis: Seven databases will be searched from their inceptions: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and Wanfang Database. Randomised controlled clinical trials (RCTs) using acupuncture to treat BPH will be included. Outcome measures included urologic symptom scores, urodynamic measures and quality-of-life scales. Adverse events will be assessed and reported for safety evaluation. Study selection and data extraction will be performed by two independent reviewers. Quality assessment (assessment of risk of bias) and data synthesis will be implemented using Review Manager (RevMan) software (ver 5.2.3).

Ethics and dissemination: Ethical approval is not necessary because this systematic review will not include specific patient data. Updates will be conducted if there is enough new evidence that may cause any change in review conclusions.

Trial registration number: PROSPERO 2014:CRD42014013645.

Strengths and limitations of this study

- Databases will be searched and trials will be screened without restriction to languages. Trials published in languages other than Chinese and English will be translated by qualified translators if they can be potentially included after reading their English titles and abstracts.
- The trial screening, data extraction and risk of bias assessment of this review will be conducted by two reviewers independently.
- Highly individualized treatment has always been characteristic of acupuncture therapy, including variation of treatment frequency, stimulation methods and courses of treatment. This may make it difficult to perform data synthesis because of clinical heterogeneity.

INTRODUCTION

Description of the condition

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate commonly encountered among older men. One histological investigation from 1984 showed that more than 40% of men in their 50s and nearly 90% of men in their 80s experience BPH.[1] However, different absolute prevalence rates were reported later in multinational population-based studies.[2,3] Lower urinary tract symptoms (LUTS) associated with BPH include obstructive symptoms (weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining), and irritative symptoms (urinary frequency, urgency and nocturia).[4,5] In the United States, treatment for BPH accounted for approximately 4.5 million physician-office visits in 2000[6] and resulted in more than 300,000 prostatectomies in 1994.[7] In China, prostate specimens from 321 deceased patients were collected from 1989 to 1992. The frequency of BPH was 13.2% among those aged 41- 50 years and increased until it reached 83.3% among those aged 81-90 years. This histological frequency of BPH in China was similar to that in Western countries.[8] Treatment for BPH includes minimally invasive therapy (MIT), surgery and medical therapy. The pharmacologic use of plants and herbs (phytotherapy) is another option for the treatment of BPH and its use has been growing steadily in some countries.[9, 10]

Description of the intervention

Acupuncture is a very important part of traditional Chinese medicine (TCM) and it has a literary history of more than 2000 years.[11]Acupuncture is a therapy that inserts needles into certain points on the body called “Xue Wei”. Centuries ago, acupuncture was developed into a discipline with its own theory and practice. TCM theorizes that acupuncture can strengthen the human body’s vital essence, called “Qi”, and remove the blockages in channels.[12]Both a World Health Organization report and a National Institutes of Health consensus conference provided lists of conditions that could be potentially

treated with acupuncture.[13.14]

How the intervention might work

Acupuncture is also helpful for a wide range of other diseases.[15] In China, BPH has been treated with acupuncture and the procedure's efficacy has been tested by some studies. In one animal model it was reported that acupuncture can neutralise pathological changes in low levels of nitric oxide synthase and impaired kidney function, which manifested as high blood urea nitrogen and serum creatinine.[16]

Why it is important to do this review

There have been some researches which provide evidence for the clinical application of acupuncture for BPH. A clinical study published recently has shown that acupuncture could improve the International Prostate Symptom Score (IPSS), maximum flow rate and residual urine volume with a treatment course of 3 months.[17] A systematic review of acupuncture and moxibustion versus western medicine for BPH was published in 2010.[18] However, its conclusion was uncertain because of the limited quality and low quantity of literature. Also, this systematic review only compared acupuncture and western medicine, which was merely a part of existing interventions for BPH. So evidence needs to be collected and analyzed for evaluation of effect and safety of acupuncture for BPH.

OBJECTIVES

We aim to conduct a systematic review, and if possible, a quantitative meta-analysis, with evidence available from randomized controlled trials into the comparative effectiveness and harms of acupuncture for men with symptomatic BPH compared with various types of control interventions. Outcomes including validated urologic symptom scores, quality-of-life score, urodynamic measures, and prostate size measurements will be included.

METHODS

The protocol of this systematic review has been registered on PROSPERO 2014 (registration number: CRD42014013645). This systematic review protocol has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[19]

Criteria for considering studies for this review

Types of studies

Parallel-group randomised controlled trials of acupuncture for BPH without any language or publication status restrictions will be included in this systematic review. Non-RCTs and uncontrolled clinical trials such as case studies will be excluded.

Types of participants

We will include studies investigating men with symptomatic BPH determined by elevated urinary symptom scores including the Boyarsky Score, [20] the American Urologic Association Symptom Index, and the IPSS.[21] There will be no restrictions on other diagnostic methods such as urinary flow rates or ultrasound. Patients with diagnoses of other diseases that may cause urinary tract symptoms such as prostatic cancer and neurogenic bladder will be excluded.

Types of interventions

For the treatment group, acupuncture therapy with needle insertion will be considered, including body acupuncture, auricular acupuncture, scalp acupuncture, and electroacupuncture. We will also include acupuncture combined with other treatments or medications, such as herbs. Excluded interventions will be any stimulation other than that of a needle, such as acupressure, seed stimulation or surface electrodes.

Control interventions will include: no intervention, placebo acupuncture, sham acupuncture, pharmacological treatments (herbal medicine or conventional medicine, such as 5-alpha reductase inhibitors and alpha

blockers), surgery or any other interventions. Placebo acupuncture includes treatments that attach a needle to the skin surface (not penetrating the skin but at the same acupoints). [22]Sham acupuncture includes: a needle placed in an area close to but not in an acupuncture point, [23] and subliminal skin electro stimulation via electrodes attached to the skin.[24]

Types of outcome measures

Primary outcome measures will be changes in urological symptoms as measured by validated urologic symptom scores, including the Boyarsky Score, [20] the American Urologic Association Symptom Score, and IPSS.[21] Secondary outcome measures will include: quality-of-life score; urodynamic measures, which are defined as changes in peak urine flow (measured in mL/s); mean urine flow (measured in mL/s) and residual urine volume (measured in mL); nocturia (measured in times per evening); and changes in prostate size (measured in cc).

Adverse events will be recorded including intolerable pain during acupuncture, bleeding during or after the session, breaking or winding of the needles, injury to organs (e.g., pneumothorax), and fainting. The number and severity of adverse events will be recorded.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases irrespective of language and publication status: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, the Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and the Wanfang Database.

Other sources

A non-electronic search will be implemented for further information including

the references of all included studies of this systematic review, bibliographic references in urological textbooks, previous reviews of acupuncture for BPH, and relevant conference proceedings.

Search strategy

Table 1 presents the search strategy for MEDLINE, a Chinese version of the same search items will be used for searching the Chinese databases.

Table 1 Ovid MEDLINE search strategy

	Search items
1	randomised controlled trial
2	controlled clinical trial
3	randomised
4	randomized
5	randomly
6	trial
7	or/1-6
8	benign prostatic hyperplasia or bph/
9	lower urinary tract symptoms or luts/
10	or/8-9
11	acupuncture/
12	acupuncture points/
13	(electroacupuncture or electro- acupuncture).tw.
14	electroacupuncture.tw.
15	acupuncture$.tw.
16	acupoints.tw.
17	meridians/
18	or /11-17
19	7 and 10 and 18

Data collection and analysis

Selection of studies

Two reviewers, WZ and WP, will independently determine the eligibility of studies. Duplicates and non-clinical trials will be removed by screening the titles and abstracts. Reviewers will read the full text if they are not sure whether the studies meet the inclusion criteria. Studies will be excluded if they are not truly randomised (Quasi-RCTs) or involve any unqualified interventions. A third party (ZL) will resolve any disagreements. Study selection is summarised in a PRISMA flow diagram（figure 1）

Data extraction and management

A data extraction form will be developed and study data will be assessed and extracted independently by two reviewers, JY and WP. The following data will be extracted from each included study: patients' demographic characteristics, including maximum, minimum, and mean age; inclusion and exclusion criteria; type, frequency, and treatment course of acupuncture therapy; and all outcomes. Type, severity, number of adverse effects, and number and reasons for dropouts, withdrawals, and patients lost to follow-up will also be recorded. Information not available in the trials will be sought from authors by e-mail, telephone or post. Extracted data will be reviewed by WZ and discrepancies will be judged by the arbitrator, ZL.

Risk of bias assessment

A tool introduced in the Cochrane Handbook for systematic reviews of interventions (V.5.1) will be used to assess a broad category of biases. This tool, available through collaboration's website and Review Manager (RevMan) software, includes five sources of bias in clinical trials and their relevant domains. The sources of bias are: selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; and reporting bias: selective outcome

reporting. Specific feature of included studies will be judged by two reviewers independently in each entry of a “risk of bias” table, where the risk of bias will be addressed as low, high or unclear.[25]

Measures of treatment effect

For dichotomous data, relative risk (RR) with corresponding 95% confidence intervals (CIs) will be used while continuous data will be expressed as mean differences (MD) with 95% CIs. MD will be used for data measured on the same scales and for which the same units are used. Standardised mean differences (SMD) will be used if studies all assess the same outcome but measure it in various ways.

Unit of analysis issues

In case unit of analysis issues arise in studies of long duration, time frames will be defined as 1 month, 3 months and 6 months to reflect short-term, medium-term and long-term follow-up respectively.

Dealing with missing data

Reviewers will try to obtain necessary information by contacting the first or corresponding authors of included trials through phone, e-mail or post if there are missing data.

Assessment of heterogeneity

We will test for statistical heterogeneity between trial results using a standard chi-squared test with a significance level of $p<0.1$ and I-squared test will be used for quantifying inconsistency among the included studies. [26]

Assessment of reporting biases

Potential reporting biases will be investigated using the funnel plot. We will use a linear regression approach to measure funnel plot asymmetry.[27]

Data synthesis

A meta-analysis will be implemented with the Cochrane Collaboration Review Manager (RevMan 5.2.3) software. All the primary and secondary outcome measures will be combined and analysed for evidence of homogeneity (P>0.1) using a fixed-effects model. Dichotomous results will be expressed as RR with 95% CIs. For continuous variables, MD, the difference between treatment and control pooled means at endpoints, and their 95% CIs, will be calculated. A random-effects model will be used if there is substantial (I^2>75%) statistical heterogeneity.

A narrative synthesis will be provided, if the meta-analysis can not be performed for all or some of expected data from included studies. Text and tables will be used to summarise and explain findings concerning efficacy and safety of acupuncture both within and between studies with reference to participants, interventions, comparators, and outcomes.

Sensitivity analysis

We will implement sensitivity analyses to explore the impacts of methodological quality and sample size on the robustness of review conclusions. Meta-analyses will be repeated after excluding studies with lower methodological quality and studies with sample sizes much bigger than those of other studies. Sensitivity analyses will be reported with a summary table and review conclusions will be interpreted with concerns for comparisons between the two meta-analyses.

Subgroup analyses

We will compare the effects between subgroups by: different acupuncture types, including electroacupuncture, elongated needle, and fire needle; different control interventions, such as herbal medicine, Western medicine and phytotherapy; and study locations.

Confidence in cumulative evidence

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology across the domains of risk of bias, consistency, directness, precision and publication bias. [28]Quality of evidence will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect).

DISCUSSION

This review aims to analyse the effects and safety of acupuncture on BPH. The systematic review of acupuncture and moxibustion versus western medicine for benign prostatic hyperplasia published by Chen and colleagues included only 6 studies from 2003 to 2006. After that, randomised controlled trials with higher methodological qualities investigating acupuncture in BPH treatment have been published. [29,30]This review will provide comprehensive and current evidence on the therapeutic effects of acupuncture on BPH, which may benefit practitioners, patients, and policy-makers.

REFERENCES

1 Berry SL, Coffey, DS, Walsh PC, *et al*. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; 132:474-79.

2 Meigs JB, Mohr B, Barry MJ, *et al*. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J Clin Epidemiol* 2001; 54:935-44.

3 Platz EA, Smit E, Curhan GC, *et al*. Prevalence of and racial/ethnic variation in lower urinary tract symptoms and noncancer prostate surgery in US men.

Urology 2002;59:877-83.

4 Christensen MM, Bruskewitz RC. Clinical manifestations of benign prostatic hyperplasia and the indications for therapeutic intervention. *Urol Clin North Am* 1990;17:509-16.

5 Caine M, Schuger L. The "capsule" in benign prostatic hypertrophy. NIH Publication No. 87-2881.Rockville, MD:US Department of Health and Human Services, 1987:221.

6 Wei JT, Calhoun EA, Jacobsen SJ. Chapter 2, Benign prostatic hyperplasia. In: Litwin MS, Saigal CS, eds. Urologic Diseases in America. Washington, DC: US Government Publishing Office, 2007:45-69.

7 McConnell JD, Barry MJ, Bruskewitz RC. Benign prostatic hyperplasia: diagnosis and treatment. Clinical Practice Guideline. No. 8, AHCPR Publication No. 94-0582 Edition. Rockville, MD: US Department of Health and Human Services 1994.

8 Gu FL, Xia TL, Kong XT. Preliminary study of the frequency of benign prostatic hyperplasia and prostatic cancer in China. *Urology* 1994; 44:688-91.

9 Bales G, Christiano AP, Kirsh E,*et al*. Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Chicago. *Urology* 1999;54:86-89.

10 Barnes PM, Powell-Griner E, McFann K, et al. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;27:1-19.

11 Huang LX. Illustrated history on Chinese acupuncture-moxibustion [In Chinese]. Qingdao,China: Qingdao publisher, 2003:186.

12 The Yellow Emperor's Classic for Internal Medicine-Ling Shu [In Chinese]. Beijing, China: People's Health Press, 1963:28.

13 Bonnerman R. Acupuncture: the World Health Organization view. Geneva, Switzerland. World Health Organization,1979.

14 NIH Consensus Conference. Acupuncture. *JAMA* 1998; 280:1518–24.

15 Xiong J. Development History and status of modern medical conditions

treated by acupuncture. *Liaoning Journal of Traditional Chinese Medicine* 2009; 36:2155-57.

16 Xu JF, Yang ZG. How acupuncture influence the NOS activity and renal function of mice with prostatic hyperplasia. *Shang Hai acupuncture Journal* 2002; 21(6):36-37.

17 Xu ZJ. Efficacy observation on benign prostatic hyperplasia treated with acupuncture and moxibustion. *Chinese acupuncture and moxibustion* 2014; 34:241-44.

18 Chen YW, Du YH, Xun J, *et al.* Acupuncture and moxibustion versus western medicine for benign prostatic hyperplasia: a systematic review. *China Journal of Traditional Chinese Medicine and Pharmacy* 2010; 25:902-06.

19 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339:b2535.

20 Boyarsky S, Jones G, Paulson DF, *et al*. A new look at bladder neck obstruction by the Food and Drug Administration regulators: guidelines for investigation of benign prostatic hypertrophy. *Trans Amer Ass Genito-Urin Surg* 1977; 68:29-32.

21 Barry MJ, Fowler FJ, Jr, O'Leary MP, *et al*. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol.* 1992; 148:1549–57.

22 Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *The Lancet* 1998; 352:364-365.

23 van Tulder MW, Cherkin DC, Berman B, *et al*. Acupuncture for low back pain. *Cochrane Library*, 2000, Issue 4.

24 Johansson BB, Haker E, von Arbin M, *et al*. Swedish Collaberation on Sensory Stimulation in Stroke. Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: a randomized, controlled trial. *Stroke* 2001; 32 :707-13.

25 Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S. eds Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0(updated March 2011). The Cochrane Collaboration, 2011. http:// www.cochrane-handbook.org (accessed Oct 2014)

26 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–58.

27 Egger M, Davey SG, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–34.

28 Balshem H , Helfanda M , Schunemann HJ , *et al.* GRADE Guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol,* 2011;64: 401-06.

29 Liu QG, Wang CY, Jiao S, *et al*. Electroacupuncture at Zhongji (CV 3) for treatment of benign hyperplasia of prostate: a multi-center ed randomized controlled study. *Chinese Acupuncture and Moxibustion*. 2008; 28:555-59.

30 Bian L, Cheng Y. Elongated needle combined with scalp needle for benign prostatic hyperplasia-a randomized controlled study. *Journal of Liaoning University of Traditional Chinese Medicine.* 2007;6:162-63.

Amendments We will provide the date of each amendment describe the change and give the rationale in case we need to amend this protocol.

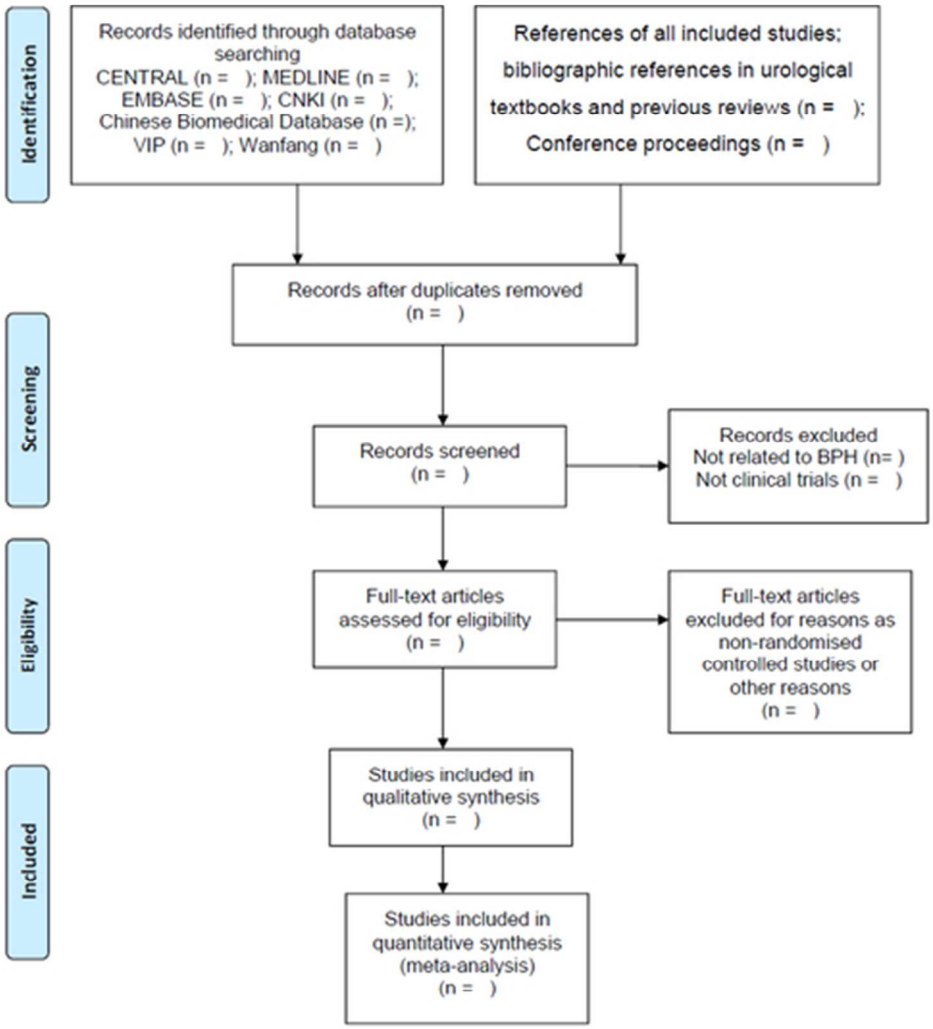
Contributors WZ is the guarantor**.** WZ and ZL contributed to the conception of this review. WZ drafted the manuscript of protocol and ZL revised it. ZL and WZ developed the search strategies while WP and JY will implement them. WP and JY will also screen the potential studies, extract data and assess quality. In case of disagreement between the two data extractors, ZL will advise on methodology and will work as arbitrator. WZ will complete data synthesis. All authors approved the final version for the publication.

Funding This work was funded by Clinical Research Fund from China Academy of Chinese Medical Sciences, Guang'anmen Hospital, with a funding reference number 84382. This fund covers the expenses including using databases, papers printing, communication and English editing. However, it will not be involved in other aspects of the review such as the design of the protocol and analysis plan.

Acknowledgements: This protocol was edited by Edanz Editing China, an editing company in Beijing for language polishing.

Competing interests None.

Figure 1 Flow diagram of the study selection process.



43x52mm (300 x 300 DPI)

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist

Section and topic	Item No	Checklist item	Reported on page#
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	16
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions,	5

Section and topic	Item No	Checklist item	Reported on page#
		comparators, and outcomes (PICO)	
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or	9

Section and topic	Item No	Checklist item	Reported on page#
		study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12