

Acupuncture and moxibustion treating lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and network meta-analysis

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Abstract

Objective: Lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) affect the quality of life of elderly individuals. Acupuncture and moxibustion are used in the clinic in China for improving LUTS symptoms due to BPH. However, there is no evidence to suggest which is the best option. We compared the efficacy of acupuncture and moxibustion to provide evidence for clinical decision-making.

Methods: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wan Fang Data, and VIP databases were searched from inception to July 2020 to identify the randomized controlled trials (RCTs) of acupuncture and moxibustion for LUTS due to BPH. Two researchers filtered studies and extracted the information independently. This study conducted a network meta-analysis using the Bayesian random method. The interventions ranking was evaluated using the surface under the cumulative ranking curve (SUCRA).

Results: We finally included 40 studies comprising 10 treating therapies and 3,655 patients with LUTS caused by BPH. In terms of the International Prostate Symptom Score, maximum urinary flow rate, and quality of life, electroacupuncture (EA) [MD = -3.6, 95% credible interval (CrI) (-5.5, -1.8), very low certainty of evidence; MD = 2.2, 95% CrI (1.1, 3.3), low certainty of evidence; MD = -1.3, 95% CrI (-2.2, -0.43), very low certainty of the evidence] may be consistently the optimal treatment compared with other interventions, with SUCRA values of 84%, 81%, and 89%, respectively.

Conclusions: Of all treatments, EA may have the best efficacy with fewer adverse events for LUTS due to BPH. The quality of evidence supporting this result is low to very low certainty of the evidence due to the limitations of primary studies; thus, more high-quality RCTs are needed for further evidence.

Keywords: Acupuncture and moxibustion, Benign prostatic hyperplasia, Lower urinary tract symptoms, Network meta-analysis, Randomized controlled trial

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases in the elderly population and is caused by the hyperplasia of prostatic stromal and epithelial

cells^[1]. Increased prevalence of BPH is associated with age^[2]. Above 70 years of age, the prevalence rate is double that at age 40 and can reach 70%^[3-4]. Symptoms of the lower urinary tract (LUTS) refer to a group of clinical manifestations that mostly result from BPH and often occur in pairs^[5-7]. The prevalence of LUTS sharply increased with aging and is also associated with many diseases, including cardiovascular disease, diabetes, neurological disease, urinary tract infections, etc^[8-9]. Increased severity of LUTS can impair quality of life (QOL) and increase the mortality risk^[10-11]. According to a study by Masaki Yoshida, LUTS have an impact on the QOL, work productivity, and healthcare in men with BPH^[12].

Currently, the treatment of BPH caused by LUTS begins with a watchful waiting approach followed by medication and surgery^[5]. Medication is the most crucial treatment for LUTS, while surgery is recommended if medication fails or BPH results in complications^[13-14]. Although many studies have claimed that medication and surgery can improve LUTS to some extent^[15-16], there were some sexual, neurological, and physical side effects of these treatments that should not be ignored^[17-18]. In addition, the treatment also leads to an increased economic burden^[19-21]. Regarding complementary and alternative medicine, we notice that acupuncture and moxibustion have certain advantages in terms of cost-effectiveness and safety^[22-23]. In addition, these treatments were widely used in clinical practice^[24-25]. Some studies suggest that

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acupuncture and moxibustion can improve patients' quality of life, sexuality, and voiding dysfunction related to LUTS during treatment^[26–28].

According to a meta-analysis for moderate to severe BPH treated with acupuncture in regard to short-term follow-up endpoints, statistical-significant changes were found in its favor^[29]. However, this study only compared acupuncture with the sham having an insufficient number of included trials, and no comparative efficacy of many types of acupuncture was described. Therefore, we conducted a network meta-analysis of LUTS due to BPH to compare the different types of acupuncture and moxibustion for the efficacy and safety.

Methods

We followed the criteria of the Reporting Standards Guidance from Preferred Reporting Items for Systematic Reviews and Meta-Analyses and its extension statement for network meta-analysis to perform our review^[30–31]. This study protocol was registered in the International Prospective Register of systematic reviews (<https://www.crd.york.ac.uk/PROSPERO/>) with ID CRD42019148394.

Eligibility criteria

We included only randomized controlled studies (RCTs), analyzing the treatment of acupuncture and moxibustion for LUTS due to BPH. There was no limit in age, with the clinical diagnosis as BPH. There was no restriction on language, region, or race. The treatment groups received acupuncture and moxibustion (electroacupuncture, acupuncture, warming acupuncture, moxibustion, warm needling, fire needle, skin needle, abdominal acupuncture, scalp acupuncture, auricular acupuncture, pressing the needle, thermal moxibustion, and so on) with or without concomitant medication (5-alpha reductase inhibitors, alpha-blockers, or their combination). The control groups received sham acupuncture, acupuncture, and moxibustion with or without concomitant medication and medication alone.

We excluded studies with a diagnosis of all urologic diseases except BPH, LUTS (caused by other conditions), inappropriate comparisons, or incomplete information. Studies involving Chinese herbal or comparisons between different medications and surgeries were also excluded. In addition, duplicated studies, reviews, and animal experiments were also excluded.

Literature search

We searched PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Data, and VIP databases from inception until July 2020 with a combination of MeSH and free terms that included: Acupuncture; Moxibustion; benign prostatic hyperplasia; lower urinary tract symptoms; RCT; and so on. We additionally searched related meta-analyses in cases of omitted trials. The detailed search information is shown in the File S1, <http://links.lww.com/AHM/A13>.

Literature screening and data extraction

Two researchers (Chen Z and Peng YY) filtered the included studies and extracted the information indepen-

dently. If there was any ambiguity in this process, we referred the issue to a third person (Liu CX) for verification. The extracted study characteristics were as follows: study characteristics (authors, publication date, research type, and country); participant information [number of enrolments, age, course of disease, and degree of International Prostate Symptom Score (IPSS)]; description and types of interventions (drug name, drug class, and combined use); description of outcomes data with changed before and after the intervention, and description of safety.

Risk of bias assessment

Two researchers (Chen Z and Jiang T) assessed the risk of bias for each study independently following the Cochrane handbook. Seven assessments were as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Disagreements were clarified by a third researcher (Liu CX)^[32].

Outcome measurements

Primary outcomes: IPSS, maximum urinary flow rate (Qmax), and QOL.

Secondary outcome: Adverse events (AEs).

Statistical analysis

We conducted a network meta-analysis with combined direct and indirect comparisons using the Bayesian random method based on the consistency assumption. Between-study heterogeneity was set with a vague prior. All primary outcomes were measured as the mean difference (MD) calculated using the posterior distribution of the model. The median and corresponding 95% credible interval (95% CrI) were reported. The models were optimized using Markov Chain Monte Carlo (MCMC) methods with the weighted sample size. We evaluated the convergence of the model by the Brooks-Gelman-Rubin method. The interventions ranking was evaluated using surface values under the cumulative ranking curve (SUCRA). We detected the potential inconsistent loops using the node-splitting analysis by comparing the direct and indirect results with the I-square statistic.

In addition, we conducted univariate meta-regression to detect potential confounding factors. Six regressors were considered as follows: sample size, age, treatment duration, course of the disease, and degree of IPSS (mild to moderate, moderate to severe). We used multiple imputations to address some missing data in the regressors.

We rated the cumulative evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and the expanded version for network meta-analysis. Regarding the risk of bias, heterogeneity, indirectness, and publication bias, direct comparisons have been rated. Combining direct and indirect evidence with further consideration of imprecision and inconsistency, we rated the network results. Moreover, we assessed the certainty of the evidence for all comparisons according to GRADE criteria and expanded the approach for network meta-analysis. Begg's and Egger's tests were used to assess publication bias.

With R 3.6.2 along with the MCMC engine JAGS (V.3.4.0) used, all estimates were calculated. Cochrane tool RevMan 5.3 was used for the risk of bias graph.

Results

Literature review

We filtered 216 titles and 125 full texts and then included 40 articles consisting of 38 Chinese and 2 English papers (File S2, <http://links.lww.com/AHM/A13>) that involved 3,655 patients with LUTS due to BPH (Figure 1). The races included in this research were all categorized as Chinese, and the region was China. The median age of the patients was 64.2 years with a range of 50 to 75 years. The median treatment duration and disease course were 5.8 weeks and 6.3 years, with ranges of 2 to 24 weeks and 1 to 21 years, respectively (Table S1, <http://links.lww.com/AHM/A13>). According to the degree of LUTS, we grouped the studies into two categories with mild to moderate and moderate to severe.

We grouped all included interventions into electroacupuncture (EA), acupuncture (A), warming acupuncture (WA), combination therapy of acupuncture and moxibustion (CTAM), sham acupuncture (SA), 5 α -reductase inhibitors (5ARI), alpha-blockers (AB), 5 α -reductase inhibitors combined with alpha-blockers (5ARI+AB), warming acupuncture combined with 5 α -reductase inhibitors (WA+5ARI), and acupuncture combined with alpha-blockers (A+AB) (Table S2, <http://links.lww.com/AHM/A13>).

All studies mentioned the word “random”, but only 16 studies reported the method of random sequence generation. Eight studies reported allocation concealment, and five studies reported blinding of participants and personnel (Figure S1, <http://links.lww.com/AHM/A13>).

Results of the network meta-analysis

International prostate symptom score

Thirty-nine studies (File S2, <http://links.lww.com/AHM/A13>) involving 3,471 patients reported changed values of IPSS after treatment, including 10 interventions, and the net plot was shown in Figure 2A. Three interventions had significant differences compared with AB [EA: MD = -3.6, 95% CrI (-5.5, -1.8); WA: MD = -3.6, 95% CrI (-7.1, -0.054); CTAM: MD = -2.6, 95% CrI (-5.2, -0.0051)] (Figure 3A). In the comparative network results, we found that EA, WA, and CTAM were statistically better than AB, 5ARI, A, and SA, respectively (Table S3, <http://links.lww.com/AHM/A13>). Regarding the SUCRA results, EA was shown to be the best intervention with a SUCRA value of 84%, followed by WA+5ARI and WA with SUCRA values of 83% and 82%, respectively (Figure 3D), and showed very low certainty of evidence in Table 1. In the node-splitting analysis, one comparison (WA vs. 5ARI, $P = 0.0098$) exhibited incoherence between direct and indirect results (Figure S2A, <http://links.lww.com/AHM/A13>).

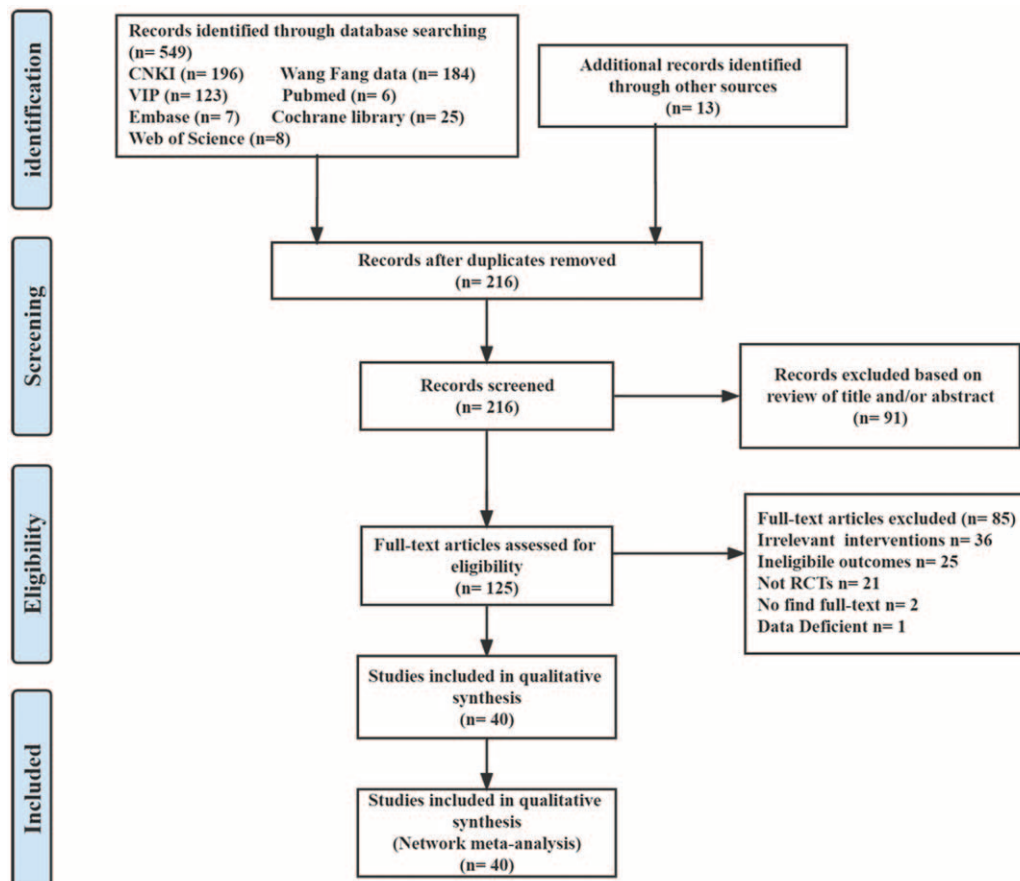


Figure 1. Summary of evidence search and selection.

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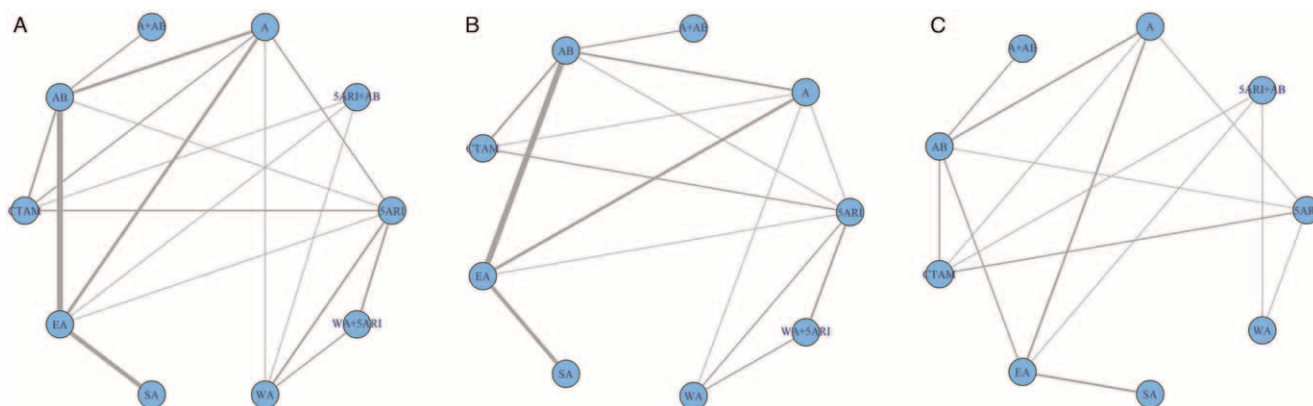


Figure 2. Network plots of primary outcomes. Interventions: 5ARI: 5 α -Reductase inhibitors; A: Acupuncture; AB: Alpha blockers; CTAM: Combination therapy of acupuncture and moxibustion; EA: Electroacupuncture; SA: Sham acupuncture; WA: Warming acupuncture.

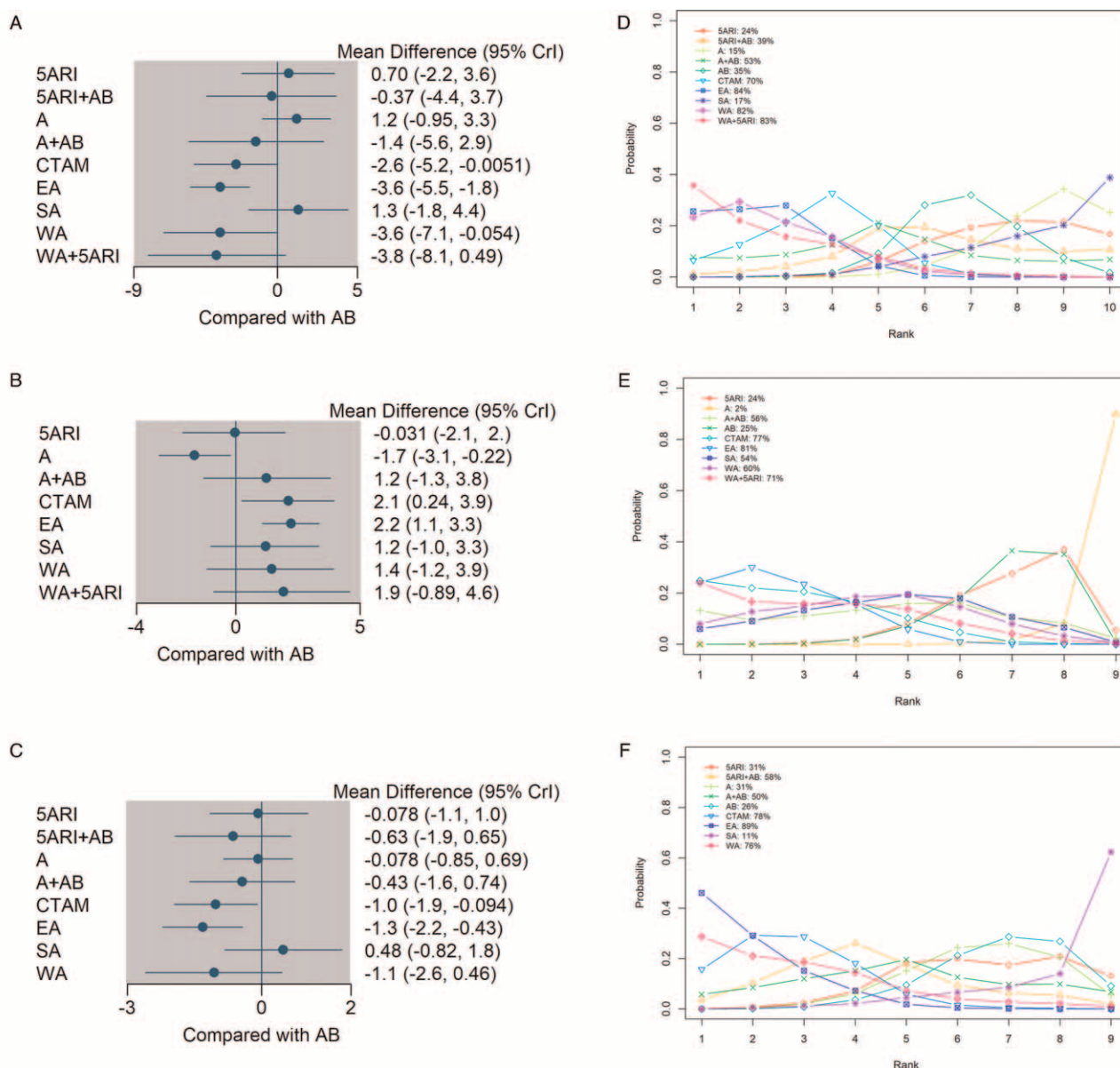


Figure 3. Forest plots and rank plots of primary outcomes. A: International prostate symptom score in forest plot; B: Maximum urinary flow rate in forest plot; C: Quality of life in forest plot; D: International prostate symptom score in rank plot; E: Maximum urinary flow rate in rank plot; F: Quality of life in rank plot. Interventions: 5ARI: 5 α -Reductase inhibitors; A: Acupuncture; AB: Alpha blockers; CTAM: Combination therapy of acupuncture and moxibustion; EA: Electroacupuncture; SA: Sham acupuncture; WA: Warming acupuncture.

Table 1
Grading of recommendations, assessment, development, and evaluation of primary outcomes.

Primary outcomes	Interventions	Quality of evidence ^a
International Prostate Symptom Score	EA vs. AB	Very low ^{1,2}
	WA+5ARI vs. AB	Very low ⁶
	WA vs. AB	Very low ⁶
	CTAM vs. AB	Very low ^{1,5}
	A+AB vs. AB	Low ¹
	5ARI+AB vs. AB	Very low ⁶
	A vs. AB	Low ^{2,5}
	5ARI vs. AB	Very low ^{1,6}
Maximum urinary flow rate	EA vs. AB	Low ¹
	CTAM vs. AB	Very low ^{1,2,6}
	WA+5ARI vs. AB	Very low ⁶
	WA vs. AB	Very low ⁶
	A+AB vs. AB	Very low ^{1,2}
	SA vs. AB	Very low ⁶
	A vs. AB	Very low ^{1,2}
	5ARI vs. AB	Very low ^{1,5,6}
Quality of life	EA vs. AB	Very low ^{1,5}
	CTAM vs. AB	Very low ^{1,6}
	5ARI+AB vs. AB	Very low ⁶
	A vs. AB	Low ¹
	WA vs. AB	Very low ⁶
	A+AB vs. AB	Very low ^{1,2}
	5ARI vs. AB	Very low ^{1,2}
	SA vs. AB	Very low ⁶

^a Reasons for downgrading direct evidence, indirect and mixed estimates: 1. Downgraded because of risk of bias; 2. Downgraded because of inconsistency; 3. Downgraded because of indirectness; 4. Downgraded because of imprecision; 5. Downgraded because of publication bias; 6. Downgraded because of intransitivity; 7. Downgraded because of incoherence. 5ARI: 5 α -Reductase inhibitors; A: Acupuncture; AB: Alpha blockers; CTAM: Combination therapy of acupuncture and moxibustion; EA: Electroacupuncture; SA: Sham acupuncture; WA: Warming acupuncture.

Maximum urinary flow rate

Thirty-one studies (File S2, <http://links.lww.com/AHM/A13>) involving 2,822 patients reported a change in Qmax score; this includes nine interventions. The net plot is shown in Figure 2B. Three interventions were significantly different, compared with AB [EA: MD=2.2, 95% CrI (1.1, 3.3); CTAM: MD=2.1, 95% CrI (0.24, 3.9); A: MD=-1.7, 95% CrI (-3.1, -0.22)] (Figure 3B). In network results, six interventions had significant differences compared with A. We found that EA and CTAM were statistically better than AB and 5RAI (Table S3, <http://links.lww.com/AHM/A13>). In the SUCRA results, EA was the best option, with SUCRA 81% (Figure 3E), showing low certainty of evidence in Table 1. In the node-splitting analysis, we found that three comparisons exhibited incoherence between direct and indirect results (A vs. 5ARI, $P=0.0341$; EA vs. A, $P=0.0063$; EA vs. AB, $P=0.0334$) (Figure S2B, <http://links.lww.com/AHM/A13>).

Quality of life

Twenty studies (File S2, <http://links.lww.com/AHM/A13>) involving 1,534 patients reported changes in QOL scores, including nine interventions, and the net plot was shown in Figure 2C. Compared with AB, two interventions had significant differences [EA: MD=-1.3, 95% CrI (-2.2,

-0.43); CTAM: MD=-1.0, 95% CrI (-1.9, -0.094)] (Figure 3C). Regarding the network results, we found that EA was statistically better than SA, AB, 5ARI, and A. CTAM had a significant difference compared with AB and SA (Table S4, <http://links.lww.com/AHM/A13>). Concerning the SUCRA results, EA is the best treatment with a SUCRA value of 89% (Figure 3F), and showing very low certainty of evidence in Table 1. In the node-splitting analysis, one comparison (EA vs. A) exhibited incoherence with a P -value of 0.0276 (Figure S2C, <http://links.lww.com/AHM/A13>).

Meta-regression

We conducted meta-regression for three primary outcomes with six regressors to detect the potential impact of confounding factors. The results are shown in Table S5, <http://links.lww.com/AHM/A13>, and no significant coefficients were found in any of the outcomes.

Publication bias

Three primary outcomes were analyzed in funnel plots with Egger's and Begg's tests to detect small-study effects and publication bias. The tests showed no significant difference in symmetry (Figure S3, <http://links.lww.com/AHM/A13>).

Adverse events

Fourteen studies (File S2, <http://links.lww.com/AHM/A13>) reported 10 AEs in total. The detailed events were as follows: EA: acupuncture pain (1 trial, 2 patients); SA: mild hematoma (4 trials, 8 patients), hematuria (2 trials, 2 patients); A: acute urinary retention (3 trials, 7 patients); AB: dizziness (2 trials, 5 patients); 5ARI: nasal obstruction (1 trial, 1 patient), dizziness (1 trial, 1 patient), sexual hypoactivity (1 trial, 3 patients), breast enlargement (1 trial, 1 patient), erectile dysfunction (1 trial, 1 patient), hematuria (1 trial, 3 patients); WA: nasal obstruction (2 trials, 4 patients), dizziness (1 trial, 1 patient), tachycardia (2 trials, 2 patients); WA+5ARI: nasal obstruction (2 trials, 2 patients), dizziness (1 trial, 2 patients), tachycardia: (2 trials, 3 patients), sexual hypoactivity (1 trial, 1 patient) (Table S6, <http://links.lww.com/AHM/A13>).

Discussion

In this study, we evaluated the efficacy and safety of acupuncture and moxibustion therapies for lower urinary tract symptoms resulting from benign prostatic hyperplasia through a network meta-analysis for the first time. Forty studies were included, and these comprised 3,655 patients and 10 grouped interventions (ie, comparisons between different types of acupuncture and moxibustion, with or without medications and their combinations).

Findings and interpretations

Regarding the IPSS, three interventions (EA, WA, CTAM) were significantly better than AB. EA had the best SUCRA value (84%), followed by WA and WA+5ARI. For Qmax, EA, CTAM, and A showed significant differences compared with AB. EA was the best therapy compared with the others with SUCRA 81%. For QOL, two

interventions (EA and CTAM) were significantly better than AB. EA showed the best SUCRA value (89%).

In the GRADE assessment, EA and others showed low- or very low-quality, which indicates that the true effect may be close to the estimate of the effect, but there is still a possibility of a difference. Regarding the safety of acupuncture and moxibustion, few AEs were found with treatment by EA, including 1 case of acupuncture pain and 1 case of bloody urine. Seven AEs were found, including 7 cases of acute urinary retention in three studies when using A. There were increased symptoms such as nasal congestion, dizziness, and tachycardia while using WA, which could be caused by smoking from moxibustion. Another symptom of sexual dysfunction was found in the study of WA combined with 5ARI. Statistically, six patients were found with dizziness, six other patients with hematuria, and four patients with sexual dysfunction occurring after taking medications (5ARI, AB) were found in six studies. Some AEs may have resulted from failed treatment, including acute urinary retention and urinary system infection.

In summary, considering the efficacy of primary outcomes and safety, EA may be the best option for LUTS due to BPH. However, given the GRADE assessment, more high-quality evidence is still needed to prove it.

Comparison with other studies

A previous meta-analysis published in China showed that treatment with acupuncture and moxibustion is effective and safe for BPH^[33]. This result is considered vague since different types of acupuncture and moxibustion were grouped into one category. By comparison, our study focused on the efficacy of different types of treatments and found that EA may be the best option compared with acupuncture and moxibustion. In addition, we used standard outcomes instead of the effectiveness rate, which was an inconsistent criterion that may cause larger heterogeneity.

Another published meta-analysis shows that EA may be more effective for BPH than SA is, and this result is similar to ours^[29]. However, this study only included several articles that did not draw convincing conclusions.

Strengths and limitations of this study

The strength of this study lies in the comparative efficacy of different types of acupuncture and moxibustion as evaluated for the first time, and EA displayed the best efficacy. In addition to using pairwise evidence, our study combined direct and indirect results with network results which provided more convincing evidence. In this study, all primary outcomes were continuous variates with standard criteria instead of the effectiveness rate with variable criteria reported in previous studies. Consequently, the heterogeneity was controllable to some extent. Given that some covariates may affect the estimates, meta-regression was conducted to test the robustness of the results.

There are several limitations to this study. Most included articles were evaluated as having low quality with a high to moderate risk of bias. Most studies failed to blind the patients and evaluators^[34]. This is mainly due to the difficulty in blinding acupuncture. Some researchers are not aware of the importance of the blind method of acupuncture. In some studies, allocation concealment was

not performed well, which affected the randomization and further affected the internal validity of the results. Thus, downgrading of pairwise results was performed in the GRADE assessment. GRADE assessments of three primary outcomes showed that most qualities of evidence were with very low to low certainty of the evidence, caused by downgrading criteria with risk of bias, inconsistency, and indirectness. Some included articles reported insufficient information on adverse events, which might have caused a risk of bias in the safety evaluation. BPH is a chronic disease in elderly patients, therefore, an accurate evaluation should include not only short-term endpoints but also long-term follow-up missing from our study. In the node-splitting analysis, we found some inconsistencies between direct and indirect results in three primary outcomes involving WA versus 5ARI for IPSS, A versus 5ARI, EA versus A, and EA versus AB for Qmax, EA versus A for QOL. Based on the evidence of all included studies, there is a lack of information on outcomes efficiency, including the control rate and economic status. Because of the included studies with limitations in a high or moderate risk of bias in most, therefore, acupuncture and moxibustion should be used with caution in clinical practice.

Conclusions

Given the efficacy of IPSS, Qmax, and QOL, EA may be the preferred option in acupuncture and moxibustion with low and very low certainty of the evidence for LUTS due to BPH. The adverse effects remained unclear; therefore, acupuncture and moxibustion should be used with caution in the clinic. Due to the low and very low certainty evidence of all interventions in the GRADE assessment, high-quality RCTs should be required to increase our confidence in this recommendation.

Conflict of interest statement

Myeong Soo Lee is the editorial board member of this journal and other authors declare no conflicts of interest.

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Author contributions

Zhe Chen, Tao Jiang, and Chunxiang Liu conceived the manuscript idea. Zhe Chen and Tao Jiang drafted the manuscript. Zhe Chen analyzed the data and interpreted the results of analysis. Zhe Chen and Yingying Peng filtered the articles and performed data extraction. Zhe Chen and Tao Jiang assessed the risk of bias. Zhe Chen and Xiaoyu Qiang performed GRADE assessment. Fengwen Yang, Haiyin Hu, Chunxiang Liu, and Myeong Soo Lee provided critical version of the manuscript. All authors contributed to the revision of the manuscript and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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