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Moxibustion for Essential Hypertension and Hypertensive Symptoms: A Systematic Review of 18 Randomized Controlled Trials

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Keywords
Moxibustion · Systematic review · Essential hypertension

Abstract

Introduction: This systematic review aims to update the evidence for moxibustion for essential hypertension. ***Methods:*** Randomized controlled trials (RCTs) comparing moxibustion versus lifestyle intervention or moxibustion plus antihypertensive drugs versus antihypertensive drugs alone were searched in 9 databases up to March 29, 2020. In meta-analyses, mean difference (MD) and proportional odds ratio (pOR) with 95% confidence intervals (CIs) was pooled for continuous and ordinal outcomes, respectively. ***Results:*** Eighteen RCTs were included, involving 1,460 patients. Moxibustion decreased systolic (MD –7.85 mm Hg, 95% CI –9.69 to –6.00, $p < 0.00001$, $I^2 = 46\%$) and diastolic (MD –4.09 mm Hg, 95% CI –5.45 to –2.73, $p < 0.0001$, $I^2 = 56\%$) blood pressures and improved the response to hypotensive treatment (pOR 2.37, 95% CI 1.49–3.75, $p = 0.0003$, $I^2 = 57\%$) significantly more than did the control treatment. Moxibustion also significantly relieved headache and dizziness but the effects changed to be statistically nonsignificant after excluding RCTs with a high risk of bias. Moxibustion did not significantly relieve insomnia and anxiety. No adverse events were reported. ***Conclusions:*** Based on the current low to moderate quality evidence, our study suggests that moxibustion may have effects on reducing blood pressure. The effects of moxibustion on typical hypertension symptoms and the long-term safety of moxibustion remain uncertain.

Moxibustion bei essenzieller Hypertonie und hypertensiven Symptomen: Eine systematische Übersicht von 18 randomisierten, kontrollierten Studien

Schlüsselwörter
Moxibustion · Systematische Übersicht · Essenzielle Hypertonie

Zusammenfassung

Einleitung: Das Ziel dieser systematischen Übersichtsarbeit war eine aktuelle Bestandsaufnahme der Evidenz zur Moxibustion bei essenzieller Hypertonie. ***Methoden:*** 9 Datenbanken wurden bis zum 29. März 2020 nach randomisierten, kontrollierten Studien (RKS) zum Vergleich der Moxibustion mit Umstellungen der Lebensgewohnheiten oder der Moxibustion plus Antihypertensiva mit Antihypertensiva allein durchsucht. In Metaanalysen

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wurden von kontinuierlichen und ordinalen Outcomes die mittleren Differenzen (MD) bzw. proportionalen Odds Ratios (pOR) gepoolt, jeweils mit 95%-Konfidenzintervall (KI). ***Ergebnisse:*** 18 RKS mit 1'460 Teilnehmern wurden eingeschlossen. Die Moxibustion führte zur Senkung des systolischen (MD –7,85 mm Hg; 95%-KI –9,69 bis –6,00; $p < 0{,}00001$; $I^2 = 46\%$) und des diastolischen Blutdrucks (MD –4,09 mm Hg; 95%-KI –5,45 bis –2,73; $p < 0{,}0001$; $I^2 = 56\%$) und zur Verbesserung des Ansprechens auf die hypotensive Therapie (pOR 2,37; 95%-KI: 1,49–3,75; $p = 0{,}0003$; $I^2 = 57\%$) in signifikantem Maße im Vergleich zur jeweiligen Kontrollbehandlung. Die Moxibustion bewirkte außerdem eine signifikante Reduktion von Kopfschmerzen und Benommenheit; diese Effekte waren jedoch nicht mehr statistisch signifikant, nachdem RKS mit hohem Bias-Risiko ausgeschlossen worden waren. Die Moxibustion bewirkte keine signifikante Besserung von Schlafstörungen und Angst. Es wurden keine unerwünschten Ereignisse beobachtet. ***Schlussfolgerungen:*** Basierend auf der derzeit vorliegenden Evidenz, die von geringer bis mäßiger Qualität ist, deutet unsere Studie darauf hin, dass Moxibustion Auswirkungen auf die Senkung des Blutdrucks haben könnte. Die Auswirkungen der Moxibustion auf typische hypertensive Symptome sowie die Langzeit-Sicherheit der Moxibustion sind noch ungeklärt.

Introduction

Essential hypertension is a global health problem affecting approximately 1.13 billion individuals in 2015, and this number is estimated to be as high as 1.56 billion in 2025 [1, 2]. As a silent killer, hypertension is asymptomatic or manifested as only a mild headache or dizziness in most patients, but it is a major risk factor for a spectrum of vascular diseases, including atherosclerosis, vascular calcification, and plaque formation, and ultimately leads to life-threatening complications, such as heart attack, stroke, and end-stage renal disease [3, 4]. According to global estimates, hypertension accounts for 47% of ischemic heart disease, 54% of stroke, and 28% of kidney failure, causing 9.4 million deaths annually [5, 6]. In the USA, direct spending on medical services for hypertension amounted to USD 42.9 billion in 2010, half of which was spent on medications [7].

The routine management of hypertension includes antihypertensive drugs and lifestyle modification (e.g., physical exercise and dietary adjustment) [8]. Although the efficacy of these treatments is well established, many challenges remain. Ten to fifteen percent of patients cannot achieve ideal blood pressure despite using 3 or more kinds of antihypertensive drugs [9]. Adverse effects, such as palpitation, fatigue, weight gain, and hyperkalemia, are also frequently experienced from taking medication, which reduces the quality of life for patients and prevents long-term compliance [10–12]. Complementary therapies with advantages in efficacy, safety and practicability are therefore required to optimize the management of hypertension.

Moxibustion, an intervention of traditional Chinese medicine that treats diseases by direct or indirect moxa heat stimulation of acupoints, is widely applied as a treatment for hypertension in China [13]. Moxibustion has proven to be effective for hypertension in studies of animals whose mechanism is associated with regulation of plasma aldosterone and atrial natriuretic peptide, activation of antioxidant capacity, and restoration of the circadian rhythm of blood pressure through the persistent heat stimulation of specific acupoints [14, 15]. Together with its empirically good safety, convenience for self-treatment, and cheap cost, moxibustion is expected to be a promising complementary approach for hypertension [16].

Two systematic reviews published in 2014 investigated the topic of moxibustion as a treatment for hypertension [17, 18]. However, these systematic reviews included substantially different randomized controlled trials (RCTs), and their conclusions were inconsistent. For example, one systematic review including 5 RCTs showed that diastolic blood pressure (DBP) was significantly more reduced in patients after undergoing moxibustion treatment than in those after undergoing no treatment/antihypertensive drugs [17], whereas another systematic review including 4 RCTs did not find such a result [18]. Moreover, the previously mentioned systematic reviews did not assess the effects of moxibustion on typical hypertension symptoms. With there being a number of newly published RCTs, we conducted this updated systematic review to inform clinical practice and contribute to the development of guidelines for moxibustion as a treatment for hypertension through a rigorous assessment of the evidence from RCTs.

Methods

The protocol of this systematic review has been registered at PROSPERO (No. CRD42019119104). The reporting for this study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist [19].

Data Sources

Nine electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, Wanfang Data, China Biomedical Literature Database, VIP, ClinicalTrials.gov, and Chinese Clinical Trial Registry were searched from the inception to March 29, 2020, to identify relevant RCTs. The search strategy used in PubMed, for instance, was as follows: (hypertension[mh] OR hypertens*[tw] OR high blood pressure*[tw]) AND (moxibustion [mh] OR moxibustion[tw] OR moxa[tw]) NOT (animals[mh] NOT humans[mh]). Additionally, we checked the references of all relevant reviews to obtain supplementations.

Eligible Criteria

Studies were eligible if they were parallel-group or crossover RCTs and assessed moxibustion as sole therapy (moxibustion vs. placebo/lifestyle interventions) or as adjunctive therapy (moxibustion + antihypertensive drug[s] vs. the same drug[s]) in patients with essential hypertension, with reporting of any outcome of interest. The diagnosis of essential hypertension should follow the American College of Cardiology criteria (i.e., systolic blood pressure (SBP) ≥130 mm Hg or DBP ≥80 mm Hg) [3]. All types of moxibustion using moxa as the burning material, except invasive moxibustion, were eligible. The eligible lifestyle interventions included control of salt and fat intake, smoking and drinking cessation, physical exercise, regular sleep, and so on. There were no restrictions on the type of antihypertensive drug used. Language and publication status were also unrestricted.

The following studies were excluded: (1) studies that included patients with secondary hypertension, gestational hypertension, or severe comorbidities (e.g., myocardial infarction or stroke); (2) studies that used nonmoxa moxibustion (e.g., electronic moxibustion) as the intervention; and (3) studies that used alternative moxibustion, other acupoint stimulation interventions (e.g., acupuncture or acupressure), or an antihypertensive drug as the control.

Outcome Assessment

Primary Outcome

Changes in SBP (mm Hg) and DBP (mm Hg).

Secondary Outcomes

(1) Response to hypotensive treatment, which was assessed according to the specified criteria in the Guidance for Clinical Research of New Chinese Medicines [20]. Specifically, the response was divided into 3 ranks: (1) marked response: DBP decrease by ≥10 mm Hg and reaching a normal range or decrease by ≥20 mm Hg; (2) moderate response: DBP decrease by 10–19 mm Hg, <10 mm Hg but reaching a normal range or SBP decrease by ≥30 mm Hg; (3) no response: none of the above conditions met.

(2) Efficacy of treatment for typical symptoms of hypertension, including dizziness, headache, anxiety, and insomnia, was assessed by a recognized scale specified in the Guidance for Clinical Research of New Chinese Medicines [20]. Each symptom was graded as none (0 points), mild (2 points), moderate (4 points), or severe (6 points).

(3) Moxibustion-related adverse events.

Study Screening and Data Collection

Two reviewers, working in pairs, performed the study screening and data extraction independently and in duplicate. They sequentially checked the titles, abstracts, and full texts to identify the RCTs that met the full set of eligibility criteria. The following information was extracted from the included RCTs: (1) baseline characteristics: authors, publication year, inclusion and exclusion criteria, numbers of patients, ages and genders of patients, types and details of moxibustion, types of control, baseline blood pressure, and comorbidities; (2) outcome data. Data from the last follow-up were extracted, except for the data from crossover trials from which we extracted data in the first phase.

Risk of Bias Assessment

We used Gordon H. Guyatt's modified version of the Cochrane Handbook tool to assess the risk of bias of the included RCTs [21, 22]. Seven aspects of risk of bias, including random sequence generation, allocation concealment, blinding of patients and caregivers, blinding of outcome assessors, data completeness, selective outcome reporting, and other bias, were assessed. For the items with ambiguous information on the risk of bias, "probably yes" or "probably no" was judged instead of "unclear" [21]. Finally, we classified the overall risk of bias for each RCT as low (all aspects showed no severe bias), moderate (1 or 2 aspects showed probably or definitely severe bias), or high (3 or more aspects showed probably or definitely severe bias). The risk of bias assessment was conducted by 2 independent reviewers, and any discrepancy was discussed or consulted with a third reviewer to reach a consensus.

Data Analysis

We used the random-effects model to pool data from the individual RCTs. Mean differences (MDs) with 95% CIs were pooled to measure continuous outcomes, which was performed by the inverse variance method. The missed SDs of change from baseline were imputed according to the baseline and last follow-up data using the Cochrane Collaboration method [22]. For ordinal outcomes (i.e., response to hypotensive treatment), a proportional odds ratio (pOR) was calculated as the effect measure using the generalized linear model in which the difference between every rank was assumed to be equal. We first calculated the log(pOR) and standard error by the PROC GENMOD program using SAS version 9.4 (SAS Institute Inc., NC, USA) [23] and then pooled the pORs by the general inverse variance method in R version 3.6.3 (St. Louis, MO, USA).

Cochran's Q test and I^2 statistics were used to assess the heterogeneity of the results quantitatively. The source of heterogeneity was further investigated by subgroup analysis stratified by 4 factors with a hypothesized effect direction: (1) type of moxibustion: direct versus indirect; larger effect in trials assessing direct moxibustion; direct moxibustion defined as moxibustion techniques that burn moxa materials on the skin directly and indirect moxibustion defined as moxibustion techniques in which there is a buffer (e.g., herb, garlic, aconite cake, ginger, etc.) between the skin and moxa [24]. (2) type of comparison: moxibustion as adjunctive therapy versus moxibustion as a sole therapy; larger effect in RCTs assessing moxibustion as an adjunctive therapy; (3) length of follow-up: ≥4 versus <4 weeks; larger effect in trials with ≥4 weeks of follow-up; (4) age: ≥60 vs. <60 years; larger effect in trials assessing patients whose mean age was ≥60 years. The first 3 factors were prespecified in the protocol and the last one was set before the data analysis was performed. Sensitivity analyses exchanging the effect model (fixed vs. random) and excluding studies with a high risk of bias were performed to validate the robustness of the results. We evaluated publication bias for the outcomes which included at least 10 RCTs according to the asymmetry of the funnel plot and Egger's test [25].

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool to appraise the quality of evidence for each outcome based on the meta-analysis results. The quality of evidence was classified as high, moderate, low, or very low according to 5 aspects of study limitations, including risk of bias, inconsistency, imprecision, indirection, and publication bias [26].

Results

Study Characteristics

The literature search yielded 1,905 records, and 18 RCTs (n = 1,460) [27–44] fulfilled the eligibility criteria after screening (Fig. 1). All RCTs were conducted in China except that one was conducted in Korea. Seven RCTs enrolled patients with a mean age <60 years, 9 enrolled

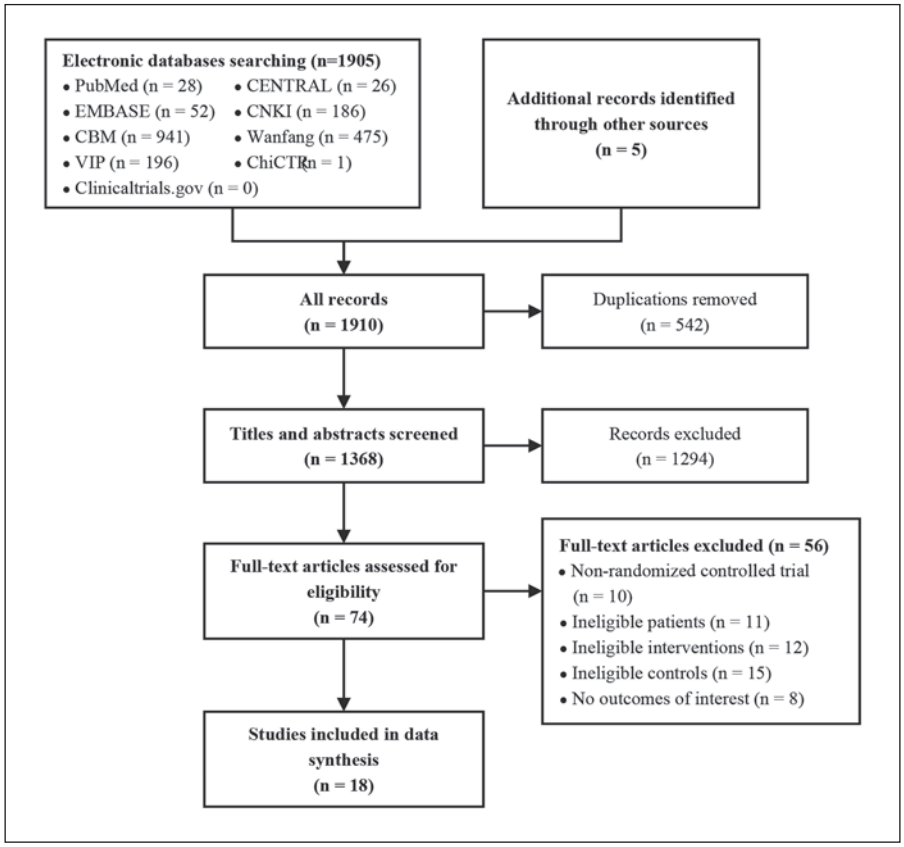

Fig. 1. Flowchart of study selection process. CENTRAL, Cochrane Central Register of Controlled Trials; CNKI, Chinese National Knowledge Infrastructure; CBM, China Biomedical Literature Database; ChiCTR, Chinese Clinical Trial Registry.

patients with a mean age of ≥60 years, and 2 did not report age information. Direct moxibustion and indirect moxibustion were used in 13 and 5 RCTs, respectively. The most common acupoints used for treating hypertension were ST36 (*Zusanli*, 11 RCTs), KI1 (*Yongquan*, 10 RCTs), LI11 (*Quchi*, 6 RCTs), GV20 (*Baihui*, 6 RCTs), and KI3 (*Taixi*, 5 RCTs). Four RCTs compared the effects between moxibustion sole therapy and lifestyle interventions/no interventions, and 14 compared moxibustion plus antihypertensive drugs versus antihypertensive drugs alone. The length of follow-up was <4 weeks in 5 RCTs and ≥4 weeks in 13 RCTs. The characteristics of the included RCTs are listed in Table 1.

Risk of Bias

Ten RCTs [27, 29, 32, 33, 35, 37, 40, 42–44] were considered to have a moderate risk of bias mainly due to inadequate implementation of allocation concealment and blindness. Eight RCTs [28, 30, 31, 34, 36, 37, 39, 41] had a high risk of bias, 9 of which had suspected flaws in random number generation, allocation concealment, and blinding of the patients, and one of which even did not report the balance of confounders at baseline. The details of the risk of bias assessment are shown in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000513701).

Blood Pressure

Thirteen RCTs (n = 1,117) [28–33, 36, 38–40, 42–44] reported data for the changes in SBP and DBP. The pooled data showed that the moxibustion group had a significantly greater reduction in SBP (MD –7.85 mm Hg, 95% CI –9.69 to –6.00, $p < 0.00001$; Fig. 2) and DBP (MD –4.09 mm Hg, 95% CI –5.45 to –2.73, $p < 0.0001$; Fig. 3) than the control group. There was moderate heterogeneity among the RCTs for both outcomes (SBP I^2 = 46%; DBP I^2 = 56%). The subgroup analysis showed that the elderly (mean age ≥60 years) patients obtained a greater reduction in both SBP (elderly vs. young: MD –9.91 vs. –6.34 mm Hg, interaction $p = 0.03$, Fig. 2) and DBP (elderly vs. young: MD –4.69 vs. –2.01 mm Hg, interaction $p = 0.38$, Fig. 3) than the younger patients (mean age <60 years) but the subgroup difference was significant in only SBP. The blood pressure-lowering effect was consistent across moxibustion methods, comparisons, and lengths of follow-up (interaction $p > 0.05$, Fig. 2, 3). The detailed results of subgroup analysis for SBP and DBP are shown in online supplementary Figures S2–S9.

Response to Hypotensive Treatment

Eleven RCTs (n = 776) [27–30, 33–37, 41, 42] reported data on the response to hypotensive treatment. The numbers of patients who had marked, moderate, and no re-

Table 1. Characteristics of included randomized controlled trials

Author	Number of patients (T/C)	Male (T/C)	Mean age (T/C), years	Type of comparison	Moxibustion intervention				Mean blood pressure in T/C, mm Hg		Follow-up period, weeks
					type	acupoints	dose per session	times per week	systolic	diastolic	
Guo et al. [27], 2020	30/30	16/17	74.4/75.1	Mox + AHD vs. AHD alone (amlodipine, metoprolol)	Indirect	ST36, ST40, LV3, KI1, SP6, CV8	30 min	7	141/137	77/78	4
Huang et al. [28], 2011	60/60	39/42	53.5/54.1	Mox + AHD vs. AHD alone (reserpine, dihydrazidazine, hydrochlorothiazide)	Direct	KI1, ST36, KI3	20 min	7	165/160	120/120	3
Huang [29], 2019	20/20	12/11	51.7/54.1	Mox vs. lifestyle intervention	Indirect	ST36, GV20, KI1	20 min	7	143/144	91/91	4
Jin and Li [30], 2014	30/30	18/14	52/54	Mox + AHD vs. AHD alone (nifedipine)	Indirect	LI11, ST36, CV5	One moxa cone	3	160/159	93/90	6
Kim et al. [31], 2005	30/31	9/11	61.5/66.1	Mox vs. lifestyle intervention	Direct	NR	NR	/	161/160	91/90	2 h
Lee [32], 2016	60/30	30/17	80.5/81.9	Mox + AHD vs. AHD alone (calcium channel blocker, angiotensin II receptor blocker)	Indirect	LI11, ST36, LI4, LV3, GV20, CV17, CV12, CV6, CV4	Five moxa cones	NR	120/116	67/69	5
Li et al. [33], 2019	45/45	22/21	64.6/65.8	Mox + AHD vs. AHD alone (enalapril)	Direct	GV20, ST36, GB39, KI1, LI11, LV3, KI3, GB21, GV14	10–15 min	7	151/151	94/94	4
Lu and Xiu [34], 2016	25/25	NR	NR	Mox + AHD vs. AHD alone (nifedipine)	Direct	ST36, KI1, LI11, KI3	30 min	7	NR	NR	3
Qiu and Li [35], 2016	32/27	11/10	55.7/54.4	Mox + AHD vs. AHD alone (amlodipine)	Direct	CV6, CV4, KI1, ST36	15 min	5	160/163	97/95	8
Tang and Gong [36], 2019	50/50	55 (all)	50.2 (all)	Mox + AHD vs AHD alone (amlodipine, captopril, metoprolol)	Direct	KI3, KI1, SP6	30 min	7	166/167	93/95	26
Wang et al. [38], 2013	80/80	29/34	68.6/60	Mox vs. lifestyle intervention	Direct	LI11, LV3, KI1, GV20, CV12, ST36, CV4, BL23	10 min	7	140/139	79/80	4
Wang et al. [37], 2018	40/40	NR	NR	Mox vs. lifestyle intervention	Direct	GV20, CV8, KI1	60 min	2	NR	NR	8
Wang [39], 2018	52/52	27/26	51/49	Mox + AHD vs. AHD alone (amlodipine)	Direct	KI1	15–20 min	14	160/161	92/93	3
Xu et al. [40], 2016	60/60	76 (all)	71.2 (all)	Mox vs. lifestyle intervention	Direct	Acupoints selected by midday-midnight method	2 days	3–4	159/158	90/88	26
Zhang et al. [41], 2007	30/21	16/11	65/62	Mox + AHD vs. AHD alone (amlodipine)	Indirect	CV8	Ten moxa cones	2	NR	NR	4
Zhao et al. [42], 2011	34/32	18/12	63.2/62.7	Mox vs. lifestyle intervention	Direct	LI11, GV20, ST36	Time when patients had heat sensitivity	/	153/154	91/90	48 h
Zheng et al. [43], 2017	29/30	11/16	56.8/59.1	Mox vs. lifestyle intervention	Direct	ST40, ST36	20 min	7	141/141	82/83	4
Zheng et al. [44], 2018	30/30	7/9	61.8/60.8	Mox + AHD vs. AHD alone (nifedipine, amlodipine)	Direct	HT7, KI3	5 min	5	137/135	82/80	4

Treatment course was equal to follow-up period in all trials. Patients in the moxibustion group received the same active drugs as the control group in all trials with add-on comparison. AHD, antihypertensive drugs; Mox, moxibustion; NR, not reported; T/C, treatment/control; /, none.

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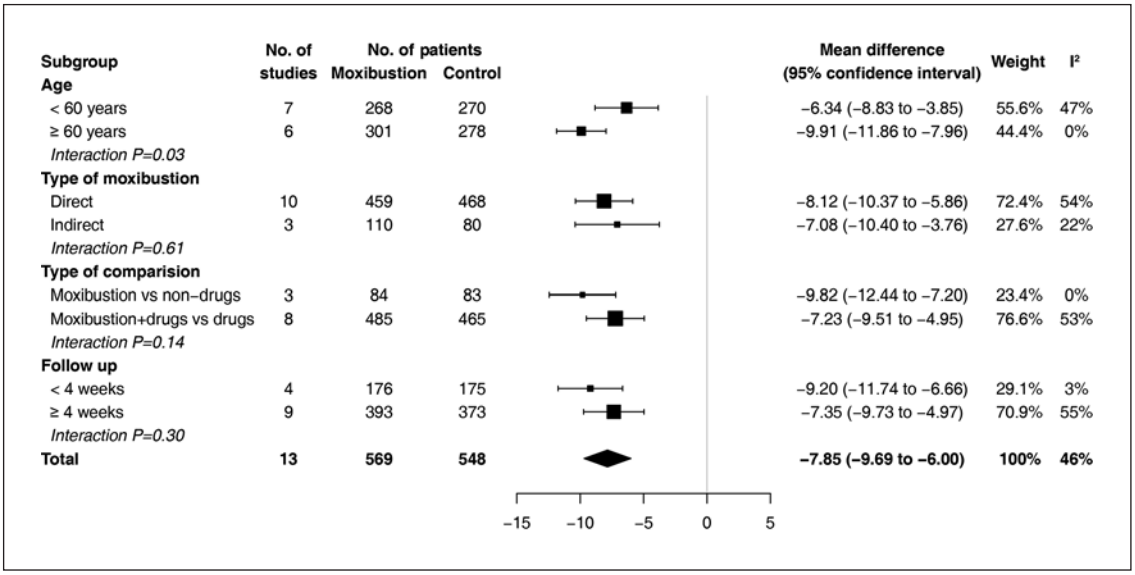

Fig. 2. Meta-analysis of changes in systolic blood pressure (mm Hg).

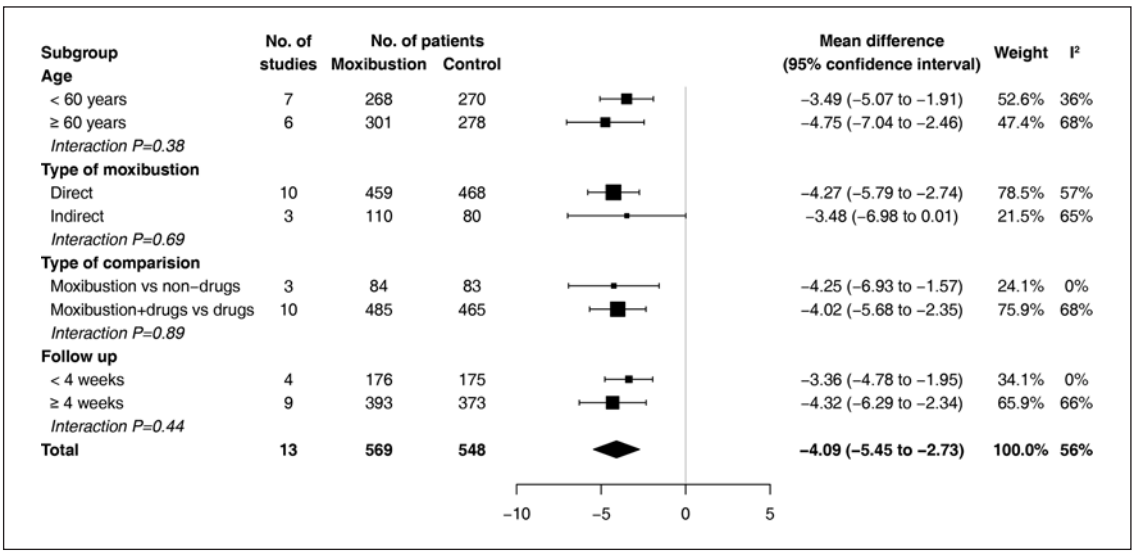

Fig. 3. Meta-analysis of changes in diastolic blood pressure (mm Hg).

sponse were 185 (46.7%), 164 (41.4%), and 47 (11.9%) in the moxibustion group and 117 (30.8%), 162 (42.6%), and 101 (26.6%) in the control group, respectively. The pooling result showed that the moxibustion group had a better response to hypotensive treatment than did the control group (pOR 2.37, 95% CI 1.49–3.75, $p = 0.0003$; Fig. 4). Heterogeneity was moderate across the RCTs ($I^2 = 57\%$). In the subgroup analysis, the RCTs with moxibustion as sole therapy presented a better response than those with moxibustion as adjunctive therapy (pOR 22.70 vs. 1.87, interaction $p = 0.0002$; Fig. 4, online suppl. Fig. S10–S13). The blood pressure-lowering effect was consistent across different ages, moxibustion methods, and lengths of follow-up.

Typical Symptoms of Hypertension

Two RCTs ($n = 139$) [37, 43] assessed the efficacy of moxibustion on the typical symptoms of hypertension, including headache, dizziness, insomnia, and anxiety, based on scale measurements. Favorable effects of moxibustion were shown for relieving headache (MD −0.62, 95% CI −0.80 to −0.45, $p < 0.0001$) and dizziness (MD −0.81, 95% CI −1.00 to −0.61, $p < 0.0001$) but not for relieving insomnia (MD 0.03, 95% CI −0.23 to 0.30, p =

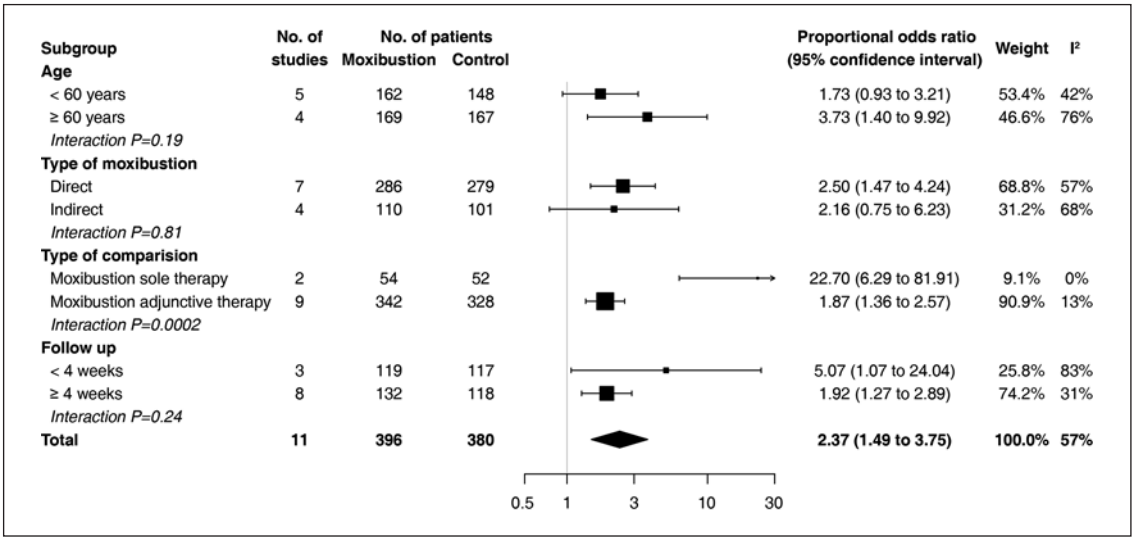

Fig. 4. Meta-analysis of response to hypotensive treatment.

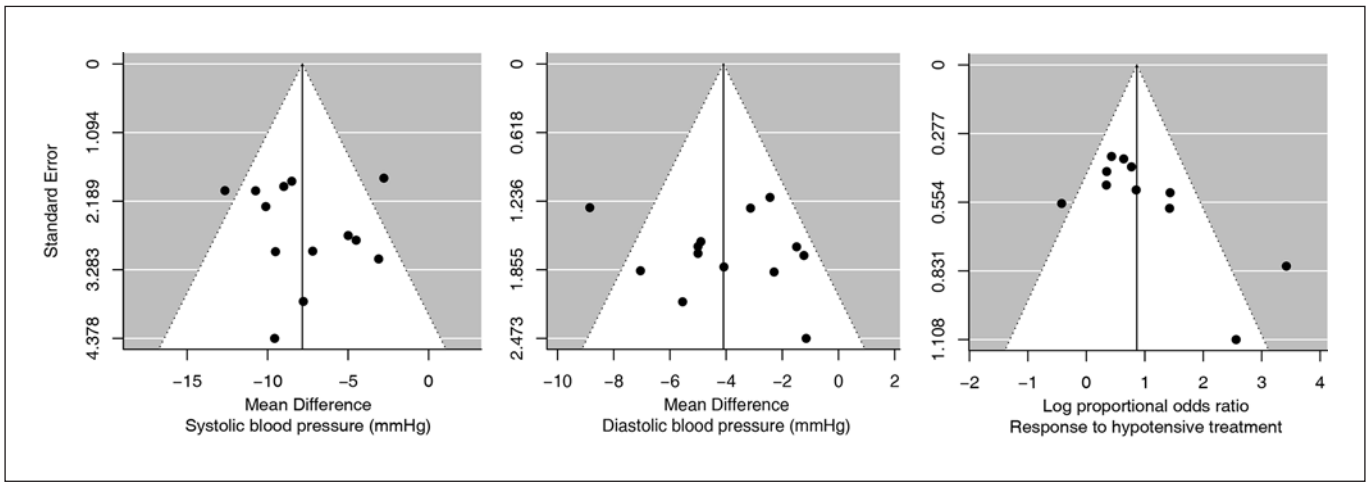

Fig. 5. Funnel plots of publication bias.

0.80) or anxiety (MD −0.02, 95% CI −0.20 to 0.16, $p = 0.83$, reported in one RCT). Heterogeneity among the studies was low for these outcomes ($I^2 = 0\%$).

Adverse Events

Three RCTs [28, 33, 37] reported the safety outcomes of moxibustion, and all found that no adverse events occurred during the follow-up.

Sensitivity Analysis

As shown in online supplementary Table S1, sensitivity analyses excluding RCTs with a high risk of bias found that the between-group differences in headache (MD −0.47, 95% CI −1.33 to 0.39) and dizziness (MD −0.41, 95% CI −1.24 to 0.42) turned out to be nonsignificant. The reductions in blood pressure were also slightly weakened after excluding the RCTs with a high risk of bias, but the direction of the results showed no changes (original analysis vs. sensitivity analysis: MD −7.85 vs. −6.72 mm Hg in SBP; −4.09 vs. −3.86 mm Hg in DBP). The sensitivity analysis that changed the type of effects model (fixed vs. random) did not show important changes for any of the outcomes.

Publication Bias

According to the results of Egger's tests, no evidence of publication bias in the SBP ($p = 0.689$) and DBP ($p = 0.636$) measurements was found, but the response to hypotensive treatment measurements had a significant publication bias ($p = 0.032$). These results were consistent with

the funnel plots being symmetrical (Fig. 5). Publication bias was not detected for symptoms of hypertension due to an insufficient number of studies that analyzed them.

Quality of Evidence

The GRADE evidence profile is shown in online supplementary Table S2. In summary, the quality of evidence was deemed to be moderate for SBP and DBP, low for the response to hypotensive treatment, insomnia, and anxiety, and very low for headache and dizziness. It was commonly downgraded by the limitations of risk of bias, inconsistency, and/or imprecision.

Discussion/Conclusion

This study was a major update of systematic reviews on moxibustion as a treatment for essential hypertension. Compared with the previous systematic reviews on this topic [17, 18], we added 14 new RCTs and increased the sample size by 1,039 patients. As a result, we found that the patients who underwent moxibustion/moxibustion plus antihypertensive drugs had a statistically significant reduction in both SBP and DBP compared to those who underwent lifestyle intervention/antihypertensive drugs, which is supported by the results of the qualitative assessment (i.e., response to hypotensive treatment), but the magnitude of the hypotensive effect was relatively small (–7.85 mm Hg in SBP and –4.09 mm Hg in DBP). The findings also suggest that the moxibustion treatment improved headaches and dizziness but not anxiety and insomnia. However, all of the findings did not establish convincing evidence, mainly owing to the moderate to high risk of bias and heterogeneity among the included RCTs.

Although the efficacy of antihypertensive drugs in patients with hypertension is well established, in fact, a significant number of patients cannot adhere to long-term medication due to adverse reactions or forgetfulness. Furthermore, according to a recent network meta-analysis of antihypertensive drugs [45], the highest effect of lowering SBP and DBP among the combination of 2 antihypertensive drugs was just –19.16 and –12.72 mm Hg, respectively. Obviously, there is also a significant number of patients with severe hypertension who cannot reach an ideal level of blood pressure despite combination therapy using multiple antihypertensive drugs. For these 2 types of patients, we believe that moxibustion can be used as a complementary therapy based on drug therapies.

Given the biological and clinical rationale, we conducted subgroup analyses stratified by 3 prespecified factors and one post hoc factor and identified a source of partial heterogeneity. The age subgroup analysis showed that the hypotensive effects on SBP were better in elderly patients than in younger patients, which may be associated with the higher baseline blood pressure of the elderly patients. A similar difference in ages has also been demonstrated in previous hypertension studies (e.g., Safe-KanArb study [46] and NHANES III study [47]). However, according to the criteria of Xin Sun et al. [48], the credibility of this subgroup finding is weakened because it is post hoc and the effect direction of individual studies is inconsistent across the age subgroups. Moreover, the subgroup analyses found that the RCTs assessing moxibustion as sole therapy presented a significantly better response to treatment than did those assessing moxibustion as adjunctive therapy, which suggested that the hypotensive effect of moxibustion may be covered by antihypertensive drugs and that the results of the response to treatment should be interpreted separately for moxibustion as sole therapy and moxibustion as adjunctive therapy. Nevertheless, the credibility of this subgroup effect is also low because the result is opposite to the hypothesized direction.

Eight out of the 18 RCTs had a high risk of bias. In the sensitive analyses excluding the RCTs with a high risk of bias, the effects of moxibustion on reducing the SBP and DBP were slightly diminished, but no directional changes were found. We consider that the risk of bias is prone to increase the hypotensive effect of moxibustion and thus lower the quality of evidence of SBP and DBP by one grade. The between-group differences in headache and dizziness were statistically nonsignificant after excluding the RCTs with a high risk of bias. Although the statistical power was substantially weakened in these sensitivity analyses due to the decrease in sample size, we still consider that the risk of bias probably distorts the estimates and thus lowers the quality of evidence by 2 grades for these outcomes. The risk of bias is mainly attributed to the lack of information on random number generation, allocation concealment, and blindness, which presents a universal phenomenon in the RCTs of traditional Chinese medicine [49, 50]. To enhance the implementation and reporting quality, we appeal the researchers to strictly follow the Consolidated Standards of Reporting Trials standards when conducting moxibustion RCTs.

There were few adverse reactions related to moxibustion in the included RCTs, which implies that moxibustion is generally safe. However, actual clinical settings are far more complicated. Hypertensive patients usually have comorbidities that impact the body's immune and repair functions, such as cardiovascular diseases, diabetes, and chronic kidney diseases, and many adverse events caused by moxibustion (e.g., burn, infection, and allergy) have been reported in these patients [51, 52]. Additionally, the toxicity of moxa smoke has long attracted criticism, but the longest follow-up in this review was 26 weeks, which is too short to investigate the ultimate impact of moxa smoke. Therefore, the long-term safety of moxibustion still requires more evidence.

There are many methodological limitations in the 3 previous systematic reviews [17, 18]. For example, both reviews [17, 18] pooled data with potential heterogeneity using a fixed-effect model, did not perform a subgroup analysis to investigate the source of heterogeneity, and interpreted the impact of the high risk of bias on the results insufficiently. Those flaws may seriously bias the estimates and probably account for the inconsistent results produced between the 2 reviews. In contrast to these reviews, we made detailed plans in advance, identified more RCTs through a high-sensitivity search strategy, assessed more outcomes related to hypertension, and appraised the quality of evidence for each outcome using the GRADE tool. For items with an unclear risk of bias, we performed further judgment by reasonable speculation, which helped accurately analyze the influence of risk of bias on the results. We designed and conducted subgroup analyses and evaluated their credibility following 5 well-recognized criteria proposed by Sun et al. [48], which reduced the impact of heterogeneity and yielded a more reasonable interpretation of the subgroup effects. Based on these methodological advantages, we believe that our systematic review provides more comprehensive and precise evidence on the effects of moxibustion as a treatment for hypertension.

The American Heart Association (AHA) summarized various alternative approaches for hypertension, in which acupuncture was not recommended based on inconsistent evidence on the efficacy – 2 small RCTs showed that acupuncture significantly reduced blood pressure, but one RCT with a relatively large sample size showed comparable effects on hypertension between acupuncture and sham acupuncture [53]. Nevertheless, we consider that it may not be appropriate to deduce the effect of moxibustion on hypertension from the AHA's recommendations on acupuncture. First, although the AHA finally did not recommend acupuncture, it was mainly because the evidence was inconsistent rather than that there is sufficient evidence to prove that acupuncture is ineffective for hypertension. Second, although both acupuncture and moxibustion belong to acupoint stimulation therapy, the mechanism of moxibustion is different from that of acupuncture. As summarized by the AHA [53], the hypotensive effect of acupuncture may mainly involve mechanical and electrical stimulations on sensory mechanoreceptors and nociceptors, which can change the level of neurotransmitters such as glutamate and acetylcholine and then attenuate sympathetic activity. Compared to acupuncture, moxibustion mainly generates thermal stimulation, supplemented by the aroma stimulation of moxa smoke. These stimulations have potential effects on regulating the active substances in the plasma such as aldosterone and atrial natriuretic peptide and hence restore the blood pressure rhythm [14, 15]. Therefore, the efficacy of moxibustion on hypertension may be different from that of acupuncture; the results of this rigorous systematic review present more objective and direct evidence regarding it.

This systematic review also has limitations. First, our subgroup analyses failed to sufficiently explain the sources of heterogeneity for SBP and DBP. Some suspicious confounders, such as the level of hypertension, complications, and methodological variations, were unable to be analyzed due to there being insufficient data. Nevertheless, for SBP and DBP, most RCTs showed a positive result favoring the moxibustion group, and few individual results showing comparable effects between the 2 groups were marginally significant or small in weight. Therefore, we consider that the moderate residual heterogeneity may only impact the accuracy but not the direction of the results. The average estimates yielded by a random-effects model are still meaningful for the clinical decision. Second, tests for publication bias are unavailable for the typical hypertensive symptoms, whereas we did not downgrade the quality of evidence rating for these outcomes in the GRADE appraisal. Third, the ultimate goal of any treatment for hypertension is to reduce the occurrence of hypertensive complications, such as ischemic heart disease, stroke, and kidney disease. Unfortunately, all RCTs were short in the length of follow-up and thus failed to report any information on the long-term efficacy and safety of moxibustion as a treatment for hypertension.

Conclusion

Moxibustion, as a single therapy or adjuvant therapy to antihypertensive drugs, may have hypotensive effects according to the current evidence, but the quality of this evidence is limited by risk of bias and heterogeneity among the included RCTs. Uncertainty regarding the effects of moxibustion on typical hypertension symptoms and the long-term safety of moxibustion remains. Well-designed RCTs and large-sample real-world studies are required to validate the antihypertensive efficacy of moxibustion and evaluate its long-term outcomes.

Statement of Ethics

This study was based on previously published studies; therefore, ethical approval is not relevant.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

X.Z. designed the study, developed search strategy, performed the data analysis, and drafted the manuscript. M.L., W.Z., Q.R., and Y.W. conducted the search, assessed risk of bias, and revised the manuscript. X.S. and Q.W. provided critical methodological advice in the revision. J.C. conceived and designed the study and developed the manuscript. J.C. and X.S. act as guarantors. All authors read and approved the final paper.

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