Complementary Therapies in Medicine (2014) 22, 187—195

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Moxibustion for essential hypertension

Xingjiang Xiong*, Wei Liu, Xiaochen Yang, Bo Feng, Jie Wang

Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

Received 8 July 2013; received in revised form 11 November 2013; accepted 18 November 2013
Available online 26 November 2013

KEYWORDS
Moxibustion;
Essential hypertension;
Systematic review

Summary The objective of this review was to assess the current clinical evidence of moxibustion for essential hypertension (EH). 7 electronic databases were searched until March 2013. Randomized clinical trials testing moxibustion, or combined with antihypertensive drugs, against antihypertensive drugs alone were included. Study selection, data extraction, quality assessment, and data analyses were conducted according to the Cochrane standards. Finally, 5 randomized trials were included. The methodological quality of the included trials was evaluated as generally low. As compared to antihypertensive drugs, no positive results in BP (RR: 1.19 [0.50, 2.81]; $P = 0.70$), was found about moxibustion. However, when combined with antihypertensive drugs, positive results in SBP (WMD: −9.57 [−10.80, −8.34]; $P < 0.00001$), DBP (WMD: −4.08 [−4.60, −3.56]; $P < 0.00001$), and BP (RR: 3.35 [1.03, 10.89]; $P = 0.04$) were found about moxibustion plus antihypertensive drugs. Most of the trials did not report adverse events, and the safety of moxibustion is still uncertain. Therefore, no confirm conclusion about the effectiveness and safety of moxibustion as adjunctive treatment for EH could be made. Rigorously designed trials are needed to confirm the evidence.

Contents

* Corresponding author at: Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beixiange 5#, Xicheng District, Beijing 100053, China. Tel.: +86 1088001817; fax: +86 1088001229.
E-mail addresses: xiongxingjiangtcm@163.com, 5administration@163.com (X. Xiong).

0965-2299
http://dx.doi.org/10.1016/j.ctim.2013.11.005

Introduction

In 1914, Fisher discovered a relationship between high blood pressure (BP) and mortality among life-insurance applicants.[1] Despite this long history of awareness, hypertension remains one of the major risk factors for cardiovascular diseases (CVDs), with an enormous burden on health care resources and the community throughout the world.[2] Across World Health Organization regions, approximately 62% of strokes and 49% of myocardial infarctions are caused by high BP.[3] It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years.[4,5] Therefore, hypertension and blood-pressure-related disease have become an emerging epidemic and important worldwide public-health challenge, especially in most low-income and middle-income countries, including China, where there is generally poor awareness, treatment, and control of the condition.[6–9] Recently, it was confirmed that a reduction of 5 mmHg in systolic blood pressure (SBP) has been associated with a 7% reduction in all-cause mortality.[10,11] A challenge faced by all countries is how to effectively reduce the harmful impact of hypertension on public health. For a long time, strategies to manage hypertension have been mainly dependent on the use of antihypertensive drugs. However, effective treatment of hypertension is limited by availability, cost, and adverse effects of conventional western medicine treatment, and these improvements have not been extended to the total population.[12] Approximately 30% of individuals with hypertension, however, may still be unaware of their condition, more than 40% of individuals with hypertension are not on treatment, and among those with diagnosed hypertension, treatment is frequently inadequate, two thirds of hypertensive patients are not being controlled to BP levels < 140/90 mmHg.[13] A certain proportion of hypertensive patients still suffered from hypertension related symptom including severe headache, dizziness, fatigue, etc. Therefore, some of them have turned to complementary and alternative medicine (CAM),[14–18] including traditional Chinese medicine (TCM),[19–29] for lowing BP and improving its related symptoms.[30–36]

Moxibustion, a traditional medical intervention of TCM, involves the application of ignited mugwort (*Artemisia vulgaris*) directly or indirectly at acupuncture points or other specific parts of the body to treat or prevent diseases.[37–39] The mechanism of moxibustion maybe related to the combination of heat (burning pain and heat stress), tar (extract), aroma (fume) and psychological stress.[40,41] According to the theory of TCM, a possible explanation for how moxibustion works is that heat could increase *qi* circulation and relieve *qi* stagnation by stimulating acupuncture points to regulate the function of meridians and visceral organs.[42] Currently, there has been a growing interest and prevalence in moxibustion worldwide.[43,44] Previous researches indicated that moxibustion may improve health-related fitness, quality of life, and psychological well-being.[45] Recent studies also suggest that it may have beneficial effects for patients with hypertension.[46–48] It is found out that moxibustion could contribute to lowing BP smoothly, restoring the circadian rhythm of BP, and improving symptoms and signs especially.[49,50] Mechanisms of moxibustion for hypertension maybe related to regulating oxygen free radical system and endocrine function of vascular endotheliocytes.[51,52] Currently, efficacy of moxibustion for essential hypertension (EH) is confirmed by a large number of published case series and randomized trials.[46,49,53–56] Moxibustion used alone or combined with antihypertensive drugs has been widely used as adjunctive treatment for EH. And until now, there is one published systematic review (SR) about moxibustion for EH in English.[57] However, as moxibustion was mainly used and researched in China, only 1 Chinese database, just Chinese National Knowledge Infrastructure (CNKI), was searched in the above SR. The other three main databases in Chinese were not included to retrieve the maximum possible number of trials of moxibustion for EH. Therefore, the role of moxibustion is still unclear due to different search strategies and databases. This study aims to assess the current clinical evidence of moxibustion as adjunctive treatment for EH.

Methods

Database and search strategies

Literature searches were conducted in Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Wanfang data, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (March 2013), EMBASE, and PubMed. We also searched the reference list of retrieved papers. As moxibustion is mainly

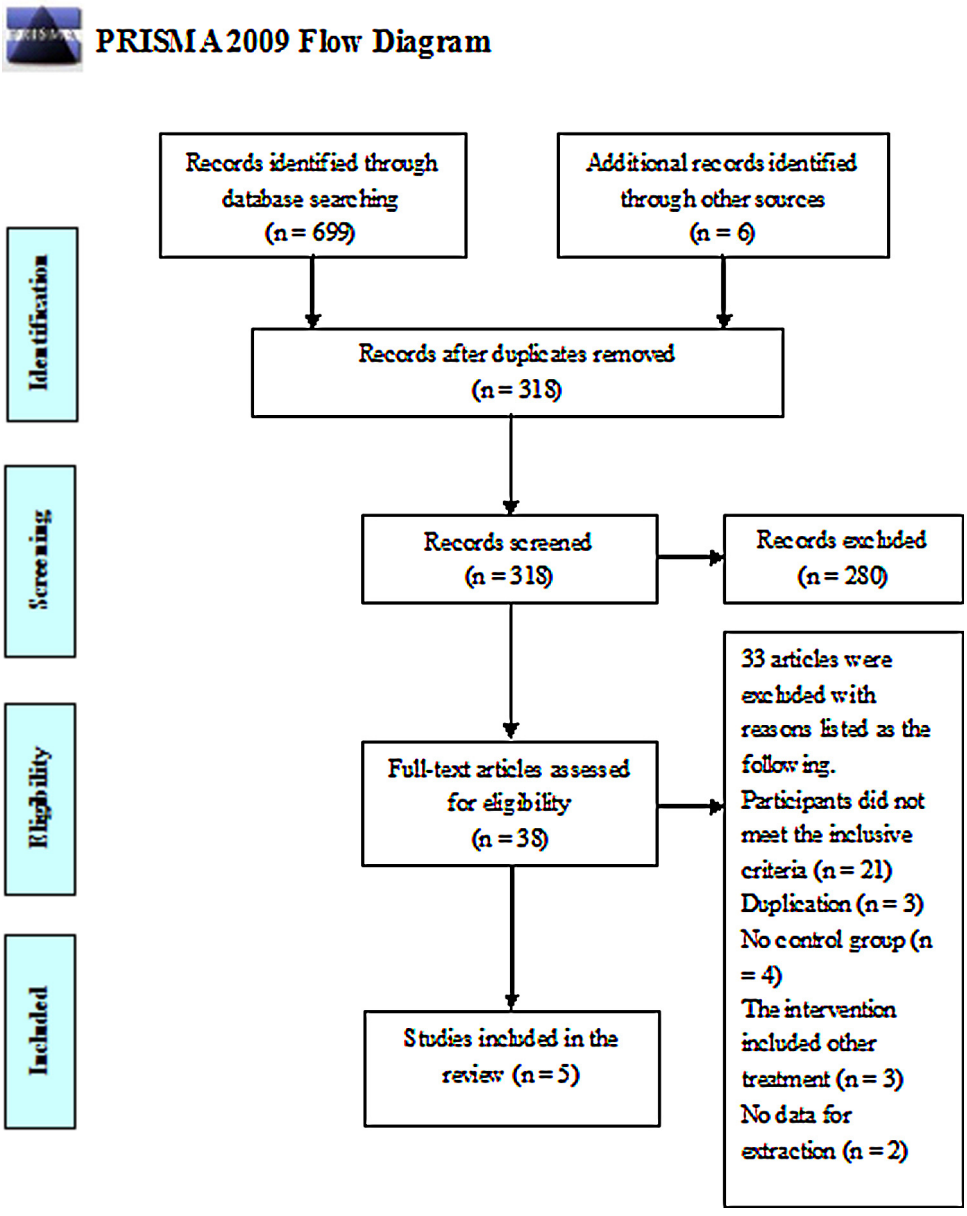

Figure 1 PRISMA 2009 flow diagram.

used and researched in China, four major databases in Chinese were all searched to retrieve the maximum possible number of trials of moxibustion for EH. All of those searches ended on 18 March 2013. Ongoing registered clinical trials were searched in the website of Chinese clinical trial registry (http://www.chictr.org/) and international clinical trial registry by U.S. National Institutes of Health (http://clinicaltrials.gov/). The following search terms were used individually or combined: 'hypertension', 'essential hypertension', 'moxibustion', 'clinical trial', and 'randomized controlled trial'. The bibliographies of included studies were searched for additional references.

Inclusion criteria

All the parallel randomized controlled trials (RCTs) of moxibustion compared with antihypertensive drugs or no treatment in patients with hypertension were included. RCTs combined moxibustion with antihypertensive drugs compared with antihypertensive drugs were included as well. There were no restrictions on population characteristics, language and publication type. The main outcome measure was BP. Duplicated publications reporting the same groups of participants were excluded.

Data extraction and quality assessment

Two authors conducted the literature searching (X.J. Xiong, X.C. Yang), study selection (X.J. Xiong, B. Feng), and data extraction (X.J. Xiong, W. Liu) independently. The extracted data included authors, title of study, year of publication, study size, age and sex of the participants, details of methodological information, treatment process, details of the control interventions, outcomes, and adverse effects

for each study. Disagreement was resolved by discussion and reached consensus through a third party (J. Wang).

The methodological quality of trials was assessed independently using criteria from the Cochrane Handbook for Systematic Review of Interventions, Version 5.1.0 (X.J. Xiong, B. Feng).[58] The items included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The quality of all the included trials was categorized to low/unclear/high risk of bias (''Yes'' for a low of bias, ''No'' for a high risk of bias, ''Unclear'' otherwise). Then trials were categorized into three levels: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias), unclear risk of bias (at least one item was in unclear).

Data synthesis

Revman 5.1 software provided by the Cochrane Collaboration was used for data analyses. Dichotomous data were presented as risk ratio (RR) and continuous outcomes as mean difference (MD), both with 95% confidence interval (CI). Heterogeneity was recognized significant when $I^2 \geq 50\%$. Fixed effects model was used if there is no significant heterogeneity of the data; random effects model was used if significant heterogeneity existed ($50\% < I^2 < 85\%$). Publication bias would be explored by funnel plot analysis if sufficient studies were found.

Result

Description of included trials

A flow chart depicted the search process and study selection (as shown in Fig. 1). After primary searches from the databases, 318 articles were screened. After reading the titles and abstracts, 280 articles of them were excluded for obviously not meeting the inclusive criteria (including literature reviews, nonclinical studies, and case series). Full texts of 38 articles were retrieved, and 33 articles were excluded with reasons listed as the following: participants did not meet the inclusive criteria ($n = 21$), duplication ($n = 3$), no control group ($n = 4$), the intervention included other treatment ($n = 3$), and no data for extraction ($n = 2$). Finally, 5 RCTs[59–63] were included. All the RCTs were published in Chinese. The characteristics of included trials were listed in Table 1.

357 patients with EH were included. 5 trials specified two diagnostic criteria of hypertension, 4 trials[59–62] used 1999 WHO-ISH guidelines for the management of hypertension (1999 WHO-ISH GMH); 1 trial[63] used Chinese Guidelines for the Management of Hypertension-2004 (CGMH-2004). Interventions included moxibustion alone, or combined with antihypertensive drugs. The controls included routine antihypertensive drugs. 2 trials[60,61] investigated moxibustion using alone versus antihypertensive drugs (including maleate enalapril and amlodipine besylate). 3 trials[59,62,63] investigated moxibustion combined with antihypertensive drugs versus antihypertensive drugs

Table 1 Characteristics and methodological quality of included studies.

Study ID	Sample	Diagnosis standard	Intervention	Control	Course	Outcome measure
Zhang et al., 2011 [59]	66	1999 WHO-ISH GMH	Moxibustion + control	Antihypertensive drugs (no detailed information)	10 days	BP
Jin et al., 2008 [60]	60	1999 WHO-ISH GMH	Moxibustion	Maleate enalapril (10 mg qd)	10 days	BP
Zhang et al., 2007 [61]	51	1999 WHO-ISH GMH	Moxibustion	Amlodipine besylate (5–10 mg qd)	30 days	BP
Zhang and Zheng, 2011 [62]	60	1999 WHO-ISH GMH	Moxibustion + control	Amlodipine besylate (5–10 mg qd)	30 days	BP
Huang et al., 2011 [63]	120	CGMH-2004	Moxibustion + control	Beijing hypotensive No.0 (1# qd)	21 days	BP

(including amlodipine besylate, Beijing hypotensive No. 0, etc.). The total treatment duration ranged from 10 to 30 days. All of the 5 trials used the BP as the outcome measure.

Methodological quality of included trials

The majority of the included trials were assessed to be of general poor methodological quality according to the predefined quality assessment criteria (Table 2). The randomized allocation of participants was mentioned in all trials; however, only 1 trial stated the methods for sequence generation with stratified sampling.[59] Insufficient information greatly limited us to judge whether or not it was conducted properly. Allocation concealment, blinding of participants and personnel, and blinding of outcome assessment were not mentioned in all trials. No trial reported drop-out. None of trials had a pre-trial estimation of sample size. We tried to contact the author for further information, however, no information has been provided to date.

Effect of the interventions

All the included trials compared moxibustion, or combined with antihypertensive drugs with antihypertensive drugs alone. A change in BP was reported in all the trials. According to the different interventions, it could be divided into 2 subgroups, including ''moxibustion versus antihypertensive drugs'' and ''moxibustion plus antihypertensive drugs versus antihypertensive drugs''.

Moxibustion versus antihypertensive drugs

2 trials[60,61] used three classes to evaluate treatment effects on BP: significant effective (DBP decreased by 10 mmHg reaching the normal range, or, DBP has not yet returned to normal, but has been reduced $\geq$20 mmHg), effective (DBP decreased to less than 10 mmHg reaching the normal range, or, DBP decreased by 10—19 mmHg, but did not reach the normal range, or, SBP decreased $\geq$30 mmHg), and ineffective (not to meet the above standards). The trial showed no significant difference between treatment and control group (RR: 1.19 [0.50, 2.81]; $P = 0.70$) (Table 3).

Moxibustion plus antihypertensive drugs versus antihypertensive drugs

2 trials[62,63] used three classes to evaluate treatment effects on BP. The trials showed significant difference between treatment and control group (RR: 3.35 [1.03, 10.89]; $P = 0.04$) (Table 3).

When it comes to SBP, 1 trial[59] showed no applicable heterogeneity in the result. Thus, fixed-effects model was used for statistical analysis. The meta-analysis showed there is significant beneficial effect on the combination group compare to antihypertensive drugs group (WMD: −9.57 [−10.80, −8.34]; $P < 0.00001$) (Table 4).

When it comes to DBP, it[59] showed no applicable heterogeneity in the result. Thus, fixed-effects model was used for statistical analysis. The meta-analysis showed there is significant beneficial effect on the combination group compare to antihypertensive drugs group (WMD: −4.08 [−4.60, −3.56]; $P < 0.00001$) (Table 5).

Table 2 Quality assessment of included randomized controlled trials.

Included trials	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Risk of bias
Zhang et al., 2011 [59]	Drawing	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Jin et al., 2008 [60]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Zhang et al., 2007 [61]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Zhang and Zheng, 2011 [62]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Huang et al., 2011 [63]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High

Table 3 Analyses of blood pressure.

Trials		Intervention (*n*/*N*)	Control (*n*/*N*)	RR [95% CI]	*P*-value
Moxibustion versus antihypertensive drugs					
Moxibustion versus maleate enalapril	1	25/30	23/30	1.52 [0.42, 5.47]	0.52
Moxibustion versus amlodipine besylate	1	21/30	17/24	0.96 [0.30, 3.12]	0.95
Meta-analysis	2	46/60	40/54	1.19 [0.50, 2.81]	0.70
Moxibustion plus antihypertensive drugs versus antihypertensive drugs					
Moxibustion plus amlodipine besylate versus amlodipine besylate	1	28/30	24/30	3.50 [0.65, 18.98]	0.15
Moxibustion plus Beijing hypotensive No. 0 versus Beijing hypotensive No. 0	1	58/60	54/60	3.22 [0.62, 16.66]	0.16
Meta-analysis	2	86/90	78/90	3.35 [1.03, 10.89]	0.04

Table 4 Analyses of systolic blood pressure.

Trials		MD [95% CI]	*P*-value
Moxibustion plus antihypertensive drugs versus antihypertensive drugs			
Moxibustion plus antihypertensive drugs versus antihypertensive drugs	1	−9.57 [−10.80, −8.34]	<0.00001
Meta-analysis	1	−9.57 [−10.80, −8.34]	<0.00001

Table 5 Analyses of diastolic blood pressure.

Trials		MD [95% CI]	*P*-value
Moxibustion plus antihypertensive drugs versus antihypertensive drugs			
Moxibustion plus antihypertensive drugs versus antihypertensive drugs	1	−4.08 [−4.60, −3.56]	<0.00001
Meta-analysis	1	−4.08 [−4.60, −3.56]	<0.00001

Publication bias

The number of trials was too small to conduct any sufficient additional analysis of publication bias.

Adverse effect

Only 1 trial mentioned the adverse effect.[63] No specific symptoms and signs were found about moxibustion in the trial. The other 4 trials[59–62] did not report it at all.

Discussion

This study aims to assess the current clinical evidence of moxibustion for EH. In this review, as compared to antihypertensive drugs, moxibustion showed similar beneficial effect for hypertension therapy; however, as adjunctive treatment, moxibustion combined with antihypertensive drugs showed more beneficial effect than antihypertensive drugs alone for EH. Although meta-analysis showed positive results, no confirm conclusion about the effectiveness and safety of moxibustion as adjunctive treatment for EH could be made based on the current evidence due to the small sample size, and poor methodological qualities of included trials. The following limitations of this review should be considered.

Firstly, the methodological quality of the included RCTs is generally low. In our review, in fact, it was impossible to find well-designed trials to evaluate efficacy of moxibustion for the management of EH. All the included trials had risk of bias in terms of design, reporting, and methodology. Inadequate reporting of study design, allocation sequence, allocation concealment, blinding, intention to treat analysis and drop outs were provided in the majority of trials. There was no definite, double blind RCTs with clear method. Randomization was mentioned but without further details in most trials, which do limit a proper judgment about how the RCTs were conducted. As no detailed information about allocation concealment could be got in all the trials, the claimed RCTs maybe not real RCTs actually. In our opinion, the credibility of current clinical evidence could be

weakened and potential selection bias might be generated. Also, no trials have reported double-blind (both blinding of participants and personnel and blinding of outcome assessment), which would directly lead to the performance bias and detection bias. We understood that it is the common problem lied in all TCM researches. Perhaps certain features associated with moxibustion such as research conditions, funding and the characterization of therapy did limit the clinical usage of double-blind. No trial reported drop-out. And most of the trials have not reported intention to treat analysis. Additionally, most of the trials were small sample size and single-center. None of the trials have reported the sample size estimation, which placed the statistical analysis's validity in doubt. Thus, whether sample size meets the requirement of the trial is still unknown. If poorly designed, all the trials would show larger differences compared with well designed trials.

Secondly, adverse effect of moxibustion has been attracted more and more attention worldwide.[64] With increasing awareness of self-care, no drug therapy and natural plants as complementary therapies are favored by people worldwide for their advantages in preventing and curing diseases. It is widely accepted that they are relative safe for various diseases in China.[65] However, with more and more reporting on the safety problem of complementary therapies, it has hence become an important focus of this systematic review.[66] In this review, there was a lack of knowledge for the reporting adverse effect of moxibustion. 4 out of 5 trials did not report the adverse effect of moxibustion at all. And only 1 trial reported adverse effect without severe symptoms and signs. Therefore, a conclusion about the safety of moxibustion cannot be made clearly. It needs to be monitored rigorously and reported appropriately in the future clinical trials.

Thirdly, publication biases may play an important role in the review. After conducting comprehensive literature searches, only trials conducted in China could be got. We tried to avoid language bias and location bias; however, potential publication bias could not be excluded completely. We have conducted extensive searches for unpublished material, but no trials were found.

In conclusion, the results of the trials included in this SR are likely to be biased by many factors due to the poor methodological qualities. The reported beneficial effect of moxibustion for lowering BP in hypertensive patients should be interpreted cautiously. Therefore, no confirm conclusion about the effectiveness and safety of moxibustion as adjunctive treatment for EH could be made.

To pave the evidence-based clinical practice, future rigorously designed randomized trials should overcome these limitations. Great attention should be paid to the following methodological issues: (1) properly implementing randomization (random sequence generation and allocation concealment); (2) appropriate methods used in double-blind (blinding of participants and personnel and blinding of outcome assessment); (3) strictly reporting dropout and intention to treat analysis; (4) attaching importance to pre-trial estimation of sample size and long-term follow-up; (5) rigorously monitoring and reporting adverse effect; (6) comprehensively reporting of the RCTs according to the recommendations of the CONSORT Statement.[67] We hope that with increasing publication of high-qualified trials, more convincing clinical evidence would confirm or refute the results.

Conflicts of interests

All authors declare that they have no conflicts of interests.

Acknowledgments

The current work was partially supported by the National Basic Research Program of China (973 Program, No. 2003CB517103) and the National Natural Science Foundation Project of China (No. 90209011). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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