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Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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ABSTRACT

Introduction: Purpose of this study protocol for a systematic review is to evaluate the effectiveness and safety of moxibustion treatment for nonspecific lower back pain patients.

Methods and Analysis: We will conduct an electronic search of several databases from their inception to November 2016, including EMBASE (OVID), MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine Database (AMED), Wanfang Database, Chongqing VIP Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure Database (CNKI), Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), the Korea Institute of Science and Technology (KISTI), and KoreaMed. Randomized controlled trials investigating any type of moxibustion treatment will be included. The primary outcome will be pain intensity and functional status/disability due to lower back pain. The secondary outcome will be a global measurement of recovery or improvement, work-related outcomes, radiographic improvement of structure, quality of life, and adverse events (presence or absence). The Cochrane risk of bias tool will be used to evaluate methodological quality. Risk ratio or mean differences with a 95% confidence interval will be used to show the effect of moxibustion therapy when a meta-analysis is available.

Ethics and Dissemination: This review will be published in a peer-reviewed journal and will be presented at an international academic conference for dissemination. Our results will provide current evidence of the effectiveness and safety of moxibustion treatment in nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and policy makers.

Trial registration number: CRD42016047468 in PROSPERO 2016

Strengths and limitations of the present study protocol

- Our review provides a systematic, objective, and comprehensive evaluation of the effectiveness and safety of moxibustion treatment in patients with lower back pain that is nonspecific.
- Our review and meta-analysis provide new and useful information for practitioners, policymakers, and patients.
- Various treatments with moxibustion and clinical outcomes reviewed in our study will help to design clinical trial studies of moxibustion treatment for nonspecific lower back pain.
- Chinese and Korean databases were searched to avoid a language bias.
- The major limitation of our study protocol is that some of the reviewed trials have small sample sizes; this limitation affects our objective and comprehensive assessment of the risks and benefits of moxibustion treatment for nonspecific lower back pain.

INTRODUCTION

More than 70% of people suffer from lower back pain in developed countries[1]. Approximately 90% of back pain is nonspecific[2], indicating that most people the pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and treating the factor that contributes to lower back pain is difficult because several co-related factors are involved, including psychological, work-related, and other individual factors[3]. Most of acute back pain is spontaneously relieved, but 20% of acute back pain patients suffer from chronic or persistent lower back pain[4]. The widely accepted definition of chronic lower back pain is a pain that persists for more than three months[5]. Even though conventional treatments such as medication or surgery have shown some efficacy against lower back pain[6,7], many lower back pain patients are dissatisfied with conventional treatment[8].

The proportion of patient using complementary and alternative medicine to treat lower back is increasing[9]. Acupuncture plays an important role in Traditional East Asian Medicine (TEAM) treatment of pain[10]. Several systematic reviews on the effectiveness and safety of acupuncture treatment in lower back pain patients have been published[11–14]. Moxibustion is an important treatment modality in TEAM treatment that stimulates acupoints with the heat energy of a burning herbal preparation[10,15]. Absorption of the therapeutically active components of the herbal preparation also contributes to the effect of moxibustion[15]. In TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at an acupoint[15]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are widely used in TEAM treatment. Systematic reviews have been published about the effectiveness of moxibustion on several disease, including insomnia, hypertension, irritable bowel syndrome, and constipation[16–19]. We conducted a preliminary search of several Chinese, English, and Korean databases for publications within the last 5 years (2011-2016)

that included randomized clinical trial data on moxibustion treatment in patients with nonspecific back pain; the results of this search revealed more than 300 articles. We excluded several articles, including animal studies, reviews, and studies of moxibustion treatment for specific back pain due to a specific pathology such as lumbar disc herniation. Ultimately, our preliminary search identified 15 relevant articles to include in our planned review[20–34].

A systematic review summarizes the evidence of relevant current clinical trial studies; this effort provides supportive information for the design of future clinical trial studies. A systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM) treatment of back pain was published in 2015[1]. This review of TCM treatment for lower back pain deals with studies involving acupuncture, acupressure, moxibustion, cupping, Gua Sha, qigong, herbal medicine, and tuina treatments. A focus on moxibustion treatment was beyond the scope of that review, as, no article on moxibustion treatment for back pain was included finally. Thus, the range of interventions that are explored in that previous review is too broad to clarify the critical factors related to moxibustion treatment of lower back pain that are of interest to practitioners and researchers; such factors include the treatment duration, position, intensity, frequency, species of moxa, various outcome parameters, and side effects of moxibustion treatment.

A systematic review of studies on the effectiveness of heat sensitive moxibustion treatment for a lumbar disc herniation has also been published[20]. However, as the prevalence of lower back pain that is secondary to a lumbar disc herniation (LDH) is low, it is not our target condition. Only 3 to 4 percent of patients with lower back pain who came to a primary clinic suffered from spinal stenosis or a lumbar disc herniation[35]. An underlying specific pathology usually cannot be identified in patients with nonspecific back pain[36]. Moreover, many patients with nonspecific back pain also suffer from musculoskeletal pain[37]. Furthermore, L5 and S1 spinal nerve root damage due to disc protrusion or degenerative

changes in the vertebrae are common causes of lower back pain in patients with a lumbar disc herniation[38].

Our preliminary search found clinical studies with various experimental designs, for example, moxibustion versus usual care or conventional treatment, moxibustion versus another TCM intervention such as (electro) acupuncture, and moxibustion adjuvant therapy with acupuncture, among others. Thus, it may be prudent to conduct a systematic review of the clinical trial studies involving various types of moxibustion treatments for nonspecific lower back pain that includes clinical outcomes. Nonetheless, we anticipate that our study will overcome the limitations of previous systematic reviews of studies involving lower back pain and TCM [1,20].

To our knowledge, a systematic review that focuses on the effectiveness of various types of moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean studies has not been published. Thus, we propose to conduct a systematic review that focuses on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower back pain. We will summarize the current evidence and provide useful information to practitioners, patients, and policymakers. A summary of the current evidence from moxibustion clinical trial studies of lower back pain will benefit the development of future moxibustion clinical trial protocols. In the present article, we describe our methods and plan for a systematic review.

Objectives

The objective of the present review is to systematically evaluate the effectiveness and safety of moxibustion treatment of nonspecific lower back pain.

METHODS

Study registration

The systematic review protocol registration number in the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines[39,40]. In addition, our review will be conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[41].

Criteria for study inclusion

Type of studies

We will include only randomized controlled trials (RCT) in this review.

Type of participants

Patients diagnosed with only nonspecific lower back pain will be included in the review. Trials studies of lower back pain due to other pathologies such as lumbar disc herniation, fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome, vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be no restriction of sex, age, ethnicity, disease duration, or disease severity.

Type of interventions

Moxibustion therapy will be compared to a placebo control, conventional treatment, no treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination with conventional treatment will be compared to conventional treatment alone. Any type of moxibustion will be included, regardless of the treatment frequency, duration, material, type,

and method. Studies involving direct moxibustion, indirect moxibustion, warm needling, moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching, and crude drug moxibustion will also be included. Research that compared different moxibustion materials, doses, or durations of moxibustion treatment will not be included. Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be included.

Primary outcomes. Pain intensity and functional status/disability will be a primary outcome. Pain intensity will be evaluated using the visual analogue scale (VAS)[42] or the numerical rating scale (NRS)[43]. Functional status/disability will be evaluated using validated measurement tools such as the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability Scale[44,45].

Secondary outcome. The secondary outcomes will include the following: 1) global measurements of recovery or improvement, such as subjective symptom improvement, the proportion of responders, overall improvement, and perceived recovery; 2) work-related outcomes, such as productivity, return to work status, and the number of absent days for work; 3) radiographic improvement of structure; 4) quality of life measurements using validated tools such as the Short Form Survey Instrument (SF-36) [46] and Euroqol-5D (EQ-5D) [47]; and 5) complications and adverse events

Search Methods

Electronic search

We will conduct an electronic search of several databases from their inception to December

2016. Four English databases will be searched, namely, EMBASE (OVID), MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied and Complementary Medicine Database (AMED); three Chinese database will be searched, namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI); and six Korean databases will be searched, namely, the Korean Medical Database (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System (OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy, lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1 present our detailed search strategy that will be specific to MEDLINE (PubMed).

Searching other resources

PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed clinical trials. We will conduct a hand search of relevant journals and their conference proceeding. Thesis and bibliographic references of included trials will also be reviewed.

Analysis

Study selection

Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in retrieved article lists from independent electronic and hand searches to exclude any obviously irrelevant articles. The full text of the remaining articles will be downloaded to assess their

eligibility for inclusion in our review according to predefined criteria. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Data extraction and management

Two review authors (J Leem and Y Cho) will read all included articles and extract data according to a predefined data sheet that includes the publication year, author, title, journal, country, hospital setting, study design, allocation concealment, randomization method, blinding, participants number, dropout number, intervention of treatment and control groups, treatment frequency and number, diagnostic criteria, disease duration, disease severity, outcome and results, and adverse event. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision. We will request via e-mail that the corresponding author of the original study send data when the results are ambiguous.

Assessment of reporting quality and risk of bias

Two review authors (J Leem and Y Cho) will independently assess the risk of bias according to the Cochrane risk of bias tool[48] outlined in the Cochrane Handbook for Systematic Reviews for Intervention[49]. Risk of bias assessment categories will include the following: (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low, high, or unclear risk of bias. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Unit of analysis

If studies measure the same outcome repeatedly, we will perform an analysis according to a timeline definition. Immediate follow-up will mean up to one week after the last intervention. Short-term follow-up will mean from one week to three months. Intermediate-term follow-up will mean from three months to 1 year after the last treatment. Long-term follow-up will mean more than 1 year after the last treatment.

Measures of a treatment effect

For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI will be used to estimate a treatment effect when the same outcome scale or method is used. Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment effect when a different outcome scale or method is used.

Managing missing data

We will contact the corresponding author of an article via e-mail to obtain any missing data. If there is no response to an e-mail, we will exclude the data from our analysis, and describe the reason and impact of this exclusion in the Discussion section.

Assessment of a reporting bias

Publication bias will be assessed visually using funnel plot asymmetry if more than 10 articles are included[49]. An Egger's regression test will be used to quantitatively evaluate funnel plot asymmetry[50].

Assessment of heterogeneity

The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that is derived from a chi-square test. The I^2 statistic will be interpreted according to the following criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will indicate the presence of substantial heterogeneity for the included studies[51]. If the I^2 statistic is more than 75%, a meta-analysis will not be conducted[52]. Instead, we will qualitatively describe the effectiveness and safety of moxibustion treatment.

Data synthesis

The Review manager (REVMAN) software for Windows will be used to perform a meta-analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3; Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt a fixed effect model in a meta-analysis.

Subgroup analysis

To identify heterogeneity between the included studies, a subgroup analysis will be conducted if there is sufficient number of articles in each subgroup. The criteria of a subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3 months) or acute lower back pain; 2) type of control group, such as placebo moxibustion, conventional treatment, other TCM treatment, and no treatment; 3) type of moxibustion, such as direct moxibustion, indirect moxibustion, warm needling moxibustion, moxa burner moxibustion, heat sensitive moxibustion, and crude drug moxibustion; 4) species of herb used

in the moxibustion treatment; and 5) treatment number, frequency, and duration.

Sensitivity analysis

If there are a sufficient number of included articles, a sensitivity analysis will be carried out after removing low quality articles to identify the robustness of a result. The methodological quality will be assessed according to the STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist[53]. After excluding low quality articles, we will conduct a second meta-analysis. The results and effect size of the two meta-analyses will be compared and discussed.

DISCUSSION

The purpose of this proposed systematic review and meta-analysis will be to evaluate the effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When compared to acupuncture research, the quantity and quality of moxibustion therapy research is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM) was published in Chinese in 2013[54], but has not been widely adopted and translated into English. A recent systematic review was published on TCM treatment of lower back pain[1]. This review included a variety of interventions that are practiced in TCM, such as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others. However, the various interventions that were included in that review have too broad of a range to appropriately evaluate the issues that are specific to moxibustion treatment of lower back pain. Moreover, it did not include any trial studies of moxibustion treatment. A systematic review has also been published regarding the effectiveness of heat sensitive moxibustion for lumbar disc herniation[20]. However, this review is not concerned with nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation.

Therefore, the protocol described here is for the first systematic review and meta-analysis on the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back pain patients. We anticipate that our review and meta-analysis will provide useful information to practitioners, policymakers, and patients.

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AUTHORS' CONTRIBUTIONS

Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for publication. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

Appendix 1 : MEDLINE(Pubmed) Search Strategy

#1 Low Back Pain/

#2 Sciatica/

#3 Radiculopathy/

#4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR aching) [TIAB]

#5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]

#6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]

#7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]

#8 {or #6-#7}

#9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]

#10 #8 and #9

#11 {or #1-#5, #10}

#12 Moxibustion/

#13 Artemisia/

#14 (moxibustion or moxabustion or moxa or artemisia or mugwort$).tw.

#15 {or #12-#14}

#16 #10 and #15

#17 randomized controlled trial [PT]

#18 controlled clinical trial [PT]

#19 randomized [TIAB]

#20 placebo [TIAB]

#21 clinical trials as topic [mesh: noexp]

#22 randomly [TIAB]

#23 trial [TI]

#24 {or #17-#23}

#25 animals [mh] NOT humans [mh]

#26 #24 NOT #25

#27 #16 and #26

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		56
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		475-479
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			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		480-483
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		480-483
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		95-140
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		155-191
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		155-191
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		194-214
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	☐		194-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		225-234
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		218-223
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		225-234
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		225-234
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		179-191
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 study level, or both; state how this information will be used in data synthesis	☐		236-245
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		281-286
	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	☐		271-286

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		consistency (e.g., I^2, Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		288-304
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		271-286
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		261-269
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		☐	Not Applicable

BMJ Open

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	lower back pain, Systematic review, meta analysis, Moxibustion, COMPLEMENTARY MEDICINE

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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ABSTRACT

Introduction: Purpose of this study protocol for a systematic review is to evaluate the effectiveness and safety of moxibustion treatment for nonspecific lower back pain patients.

Methods and Analysis: We will conduct an electronic search of several databases from their inception to December 2016, including EMBASE (OVID), MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine Database (AMED), Wanfang Database, Chongqing VIP Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure Database (CNKI), Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), the Korea Institute of Science and Technology (KISTI), and KoreaMed. Randomized controlled trials investigating any type of moxibustion treatment will be included. The primary outcome will be pain intensity and functional status/disability due to lower back pain. The secondary outcome will be a global measurement of recovery or improvement, work-related outcomes, radiographic improvement of structure, quality of life, and adverse events (presence or absence). The Cochrane risk of bias tool will be used to evaluate methodological quality. Risk ratio or mean differences with a 95% confidence interval will be used to show the effect of moxibustion therapy when it is possible to conduct a meta-analysis.

Ethics and Dissemination: This review will be published in a peer-reviewed journal and will be presented at an international academic conference for dissemination. Our results will provide current evidence of the effectiveness and safety of moxibustion treatment in nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and policy makers.

Trial registration number: CRD42016047468 in PROSPERO 2016

Strengths and limitations of the present study protocol

- Our review provides a systematic, objective, and comprehensive evaluation of the effectiveness and safety of moxibustion treatment in patients with lower back pain that is nonspecific.
- Our review and meta-analysis provide new and useful information for practitioners, policymakers, and patients.
- Various treatments with moxibustion and clinical outcomes reviewed in our study will help to design clinical trial studies of moxibustion treatment for nonspecific lower back pain.
- Chinese and Korean databases will be searched to avoid a language bias.
- The major limitation of our study protocol is that some of the reviewed trials may have small sample sizes; this limitation affects our objective and comprehensive assessment of the risks and benefits of moxibustion treatment for nonspecific lower back pain.

INTRODUCTION

More than 70% of people suffer from lower back pain in developed countries[1]. Approximately 90% of back pain is nonspecific[2], indicating that most people the pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and treating the factor that contributes to lower back pain is difficult because several co-related factors are involved, including psychological, work-related, and other individual factors[3]. Back pain is spontaneously relieved, but 5 ~ 20% of acute back pain patients suffer from chronic or persistent lower back pain[4–7]. The widely accepted definition of chronic lower back pain is a pain that persists for more than three months[8]. Even though conventional treatments such as medication or surgery have shown some efficacy against lower back pain[9,10], many lower back pain patients are dissatisfied with conventional treatment[11].

The proportion of patients using complementary and alternative medicine to treat lower back is increasing[12]. Acupuncture plays an important role in Traditional East Asian Medicine (TEAM) treatment of pain[13]. Several systematic reviews on the effectiveness and safety of acupuncture treatment in lower back pain patients have been published[14–17]. Moxibustion is an important treatment modality in TEAM treatment that stimulates acupoints with the heat energy of a burning herbal preparation[13,18]. Absorption of the therapeutically active components of the herbal preparation also contributes to the effect of moxibustion[18]. In TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at an acupoint[18]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are widely used in TEAM treatment. Systematic reviews have been published about the effectiveness of moxibustion in several diseases, including insomnia, hypertension, irritable bowel syndrome, and constipation[19–22]. However, systematic review that focuses especially on the effectiveness of moxibustion treatment in nonspecific lower back pain has not been published yet.

A systematic review summarizes the evidence of relevant current clinical trial studies; this effort provides supportive information for the design of future clinical trial studies. A systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM) treatment of back pain was published in 2015[1]. This review of TCM treatment for lower back pain deals with studies involving whole TCM interventions such as acupuncture, acupressure, moxibustion, cupping, Gua Sha, qigong, herbal medicine, and tuina treatments. A focus on moxibustion treatment was beyond the scope of that review, as, no article on moxibustion treatment for back pain was included finally. Thus, the range of interventions that are explored in that previous review is too broad to clarify the critical factors related to moxibustion treatment of lower back pain that are of interest to practitioners and researchers; such factors include the treatment duration, position, intensity, frequency, species of moxa, various outcome parameters, and side effects of moxibustion treatment. A systematic review of studies on the effectiveness of heat sensitive moxibustion treatment for a lumbar disc herniation has also been published[23]. However, as the prevalence of lower back pain that is secondary to a lumbar disc herniation (LDH) is low, it is not our target condition. Only 3 to 4 percent of patients with lower back pain who came to a primary clinic suffered from spinal stenosis or a lumbar disc herniation[24]. L5 and S1 spinal nerve root damage due to disc protrusion or degenerative changes in the vertebrae are common causes of lower back pain in patients with a lumbar disc herniation[25]. Hence, nonspecific lower back pain and LDH have different pathophysiologies.

Our preliminary search on moxibustion treatment for lower back pain found several clinical studies with various experimental designs; for example, moxibustion versus usual care or conventional treatment, moxibustion versus another TCM intervention such as (electro) acupuncture, and moxibustion adjuvant therapy with acupuncture, among others. Thus, we believe that our study will overcome the limitations of previous systematic reviews of studies

involving lower back pain and TCM [1,23].

To our knowledge, a systematic review that focuses on the effectiveness of various types of moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean studies has not been published. Thus, we propose to conduct a systematic review that focuses on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower back pain. We will summarize the current evidence and provide useful information to practitioners, patients, and policymakers. A summary of the current evidence from moxibustion clinical trial studies of lower back pain will benefit the development of future moxibustion clinical trial protocols. In the present article, we describe our methods and plan for a systematic review.

Objectives

The objective of the present review is to systematically evaluate the effectiveness and safety of moxibustion treatment compared to placebo control, conventional treatment, or no treatment in nonspecific lower back pain patients evaluated by pain intensity and functional status/disability.

METHODS

Study registration

The systematic review protocol registration number in the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines[26,27]. In addition, our review will be conducted in compliance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) statement guidelines[28].

Criteria for study inclusion

Type of studies

We will include only randomized controlled trials (RCT) in this review. Several Chinese trials do not provide detailed description of the randomization method used. We will include such studies if the authors have mentioned about the randomization method used (随机). However, we will grade these studies as high in the "risk of bias assessment" if detailed description on the randomization process is not provided. Furthermore, if an incorrect randomization method such as coin toss was used, the study will not be included.

Type of participants

Patients diagnosed with only nonspecific lower back pain will be included in the review. Trials studies of lower back pain due to other pathologies such as lumbar disc herniation, fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome, vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be no restriction of sex, age, ethnicity, disease duration, or disease severity.

Type of interventions

Moxibustion therapy will be compared to a placebo control, conventional treatment, no treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination with conventional treatment will be compared to conventional treatment alone. Any type of moxibustion will be included, regardless of the treatment frequency, duration, material, type, and method. Studies involving direct moxibustion, indirect moxibustion, warm needling,

moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching, and crude drug moxibustion will also be included. Research that compared different moxibustion materials, doses, or durations of moxibustion treatment will not be included. Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be included.

Primary outcomes.

Pain intensity and functional status/disability will be a primary outcome.

Chief complaints of nonspecific low back pain are pain and functional disability. Moreover, there are no objective biomarkers and parameters to evaluate lower back pain. Therefore, we selected pain intensity and functional status/disability as primary outcomes. These primary outcomes were also widely used in several of the previous systematic reviews on various interventions for lower back pain[1,29–33]. Other important outcomes used in these reviews were considered secondary outcomes of our review. Pain intensity will be evaluated using the visual analogue scale (VAS)[34] or the numerical rating scale (NRS)[35]. As VAS is continuous data and NRS is dichotomous data, VAS and NRS will not be mixed in the meta-analysis. Functional status/disability will be evaluated using validated measurement tools such as the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability Scale[36,37].

Secondary outcome.

The secondary outcomes will include the following: 1) global measurements of recovery or improvement, such as subjective symptom improvement, the proportion of responders, overall improvement, and perceived recovery; 2) work-related outcomes, such as productivity,

return to work status, and the number of absent days for work; 3) radiographic improvement of structure; 4) quality of life measurements using validated tools such as the Short Form Survey Instrument (SF-36) [38] and Euroqol-5D (EQ-5D) [39]; and 5) complications and adverse events

Search Methods

Electronic search

We will conduct an electronic search of several databases from their inception to December 2016. Four English databases will be searched, namely, EMBASE (OVID), MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied and Complementary Medicine Database (AMED); three Chinese database will be searched, namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI); and six Korean databases will be searched, namely, the Korean Medical Database (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System (OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy, lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1 present our detailed search strategy that will be specific to MEDLINE (PubMed).

Searching other resources

PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed

clinical trials. We will conduct a hand search of relevant journals and their conference proceeding. Thesis and bibliographic references of included trials will also be reviewed.

Analysis

Study selection

Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in retrieved article lists from independent electronic and hand searches to exclude any obviously irrelevant articles. The full text of the remaining articles will be downloaded to assess their eligibility for inclusion in our review according to predefined criteria. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Data extraction and management

Two review authors (J Leem and Y Cho) will read all included articles and extract data according to a predefined data sheet that includes the publication year, author, title, journal, country, hospital setting, study design, allocation concealment, randomization method, blinding, participants number, dropout number, intervention of treatment and control groups, treatment frequency and number, diagnostic criteria, disease duration, disease severity, outcome and results, and adverse event. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision. We will request via e-mail that the corresponding author of the original study send data when the results are ambiguous.

Assessment of reporting quality and risk of bias

Two review authors (J Leem and Y Cho) will independently assess the risk of bias according

to the Cochrane risk of bias tool[40] outlined in the Cochrane Handbook for Systematic Reviews for Intervention[41]. Risk of bias assessment categories will include the following: (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low, high, or unclear risk of bias. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Unit of analysis

If studies measure the same outcome repeatedly, we will perform an analysis according to a timeline definition. Immediate follow-up will mean up to one week after the last intervention. Short-term follow-up will mean from one week to three months. Intermediate-term follow-up will mean from three months to 1 year after the last treatment. Long-term follow-up will mean more than 1 year after the last treatment. If two or more moxibustion treatment arm exist, the number of control group patients will be divided by the number of moxibustion treatment groups and will be synthesized in a meta-analysis

Measures of a treatment effect

For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI will be used to estimate a treatment effect when the same outcome scale or method is used. Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment effect when a different outcome scale or method is used.

Managing missing data

We will contact the corresponding author of an article via e-mail to obtain any missing data. If there is no response to an e-mail, we will exclude the data from our analysis, and describe the reason and impact of this exclusion in the Discussion section.

Assessment of a reporting bias

Publication bias will be assessed visually using funnel plot asymmetry if more than 10 articles are included[41]. An Egger's regression test will be used to quantitatively evaluate funnel plot asymmetry[42].

Assessment of heterogeneity

The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that is derived from a chi-square test. The I^2 statistic will be interpreted according to the following criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will indicate the presence of substantial heterogeneity for the included studies[43]. If the I^2 statistic is more than 75%, a meta-analysis will not be conducted[44]. Instead, we will qualitatively describe the effectiveness and safety of moxibustion treatment. If the I^2 statistic belongs to both heterogeneity categories, we will use both adjectives. For example, if I^2 statistic is 55%, we will express the heterogeneity as "moderate to substantial heterogeneity."

Data synthesis and grading of quality of evidence

The Review manager (REVMAN) software for Windows will be used to perform a meta-analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3;

Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt a fixed effect model in a meta-analysis. If we are unable to conduct meta-analysis due to lack of clinical studies or heterogeneity, we will present the effect size and 95% confidence interval of every outcome in each clinical trial and describe the meaning of important results in the discussion section qualitatively. To summarize the findings of the meta-analysis and describe the strength of evidence, we will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach[41].

Subgroup analysis

To identify heterogeneity between the included studies, a subgroup analysis will be conducted if there is sufficient number of articles in each subgroup. The criteria of a subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3 months) or acute lower back pain (we will conduct a subgroup analysis according to disease duration even though there are not sufficient number of included studies); 2) type of control group, such as placebo moxibustion, conventional treatment, other TCM treatment, and no treatment; 3) type of moxibustion, such as direct moxibustion, indirect moxibustion, warm needling moxibustion, moxa burner moxibustion, heat sensitive moxibustion, and crude drug moxibustion; 4) species of herb used in the moxibustion treatment; and 5) treatment number, frequency, and duration.

Sensitivity analysis

If there are a sufficient number of included articles, a sensitivity analysis will be carried out after removing low quality articles to identify the robustness of a result. The methodological quality will be assessed according to the “risk of bias” tool[40]. After excluding low quality

articles that have more than three "risk of bias categories" graded as "high risk of bias," we will conduct a second meta-analysis. The results and effect size of the two meta-analyses will be compared and discussed.

DISCUSSION

The purpose of this proposed systematic review and meta-analysis will be to evaluate the effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When compared to acupuncture research, the quantity and quality of moxibustion therapy research is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM) was published in Chinese in 2013[45], but has not been widely adopted and translated into English. A recent systematic review was published on TCM treatment of lower back pain[1]. This review included a variety of interventions that are practiced in TCM, such as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others. However, the various interventions that were included in that review have too broad of a range to appropriately evaluate the issues that are specific to moxibustion treatment of lower back pain. Moreover, it did not include any trial studies of moxibustion treatment. A systematic review has also been published regarding the effectiveness of heat sensitive moxibustion for lumbar disc herniation[23]. However, this review is not concerned with nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation. Therefore, the protocol described here is for the first systematic review and meta-analysis on the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back pain patients. We anticipate that our review and meta-analysis will provide useful information to practitioners, policymakers, and patients.

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AUTHORS' CONTRIBUTIONS

Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for publication. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

Appendix 1 :

[MEDLINE(Pubmed) Search Strategy]

#1 Low Back Pain/

#2 Sciatica/

#3 Radiculopathy/

#4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR aching) [TIAB]

#5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]

#6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]

#7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]

#8 {or #6-#7}

#9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]

#10 #8 and #9

#11 {or #1-#5, #10}

#12 Moxibustion/

#13 Artemisia/

#14 (moxibustion or moxabustion or moxa or artemisia or mugwort$).tw.

#15 {or #12-#14}

#16 #11 and #15

#17 randomized controlled trial [PT]

#18 controlled clinical trial [PT]

#19 randomized [TIAB]

#20 placebo [TIAB]

#21 clinical trials as topic [mesh: noexp]

#22 randomly [TIAB]

#23 trial [TI]

#24 {or #17-#23}

#25 animals [mh] NOT humans [mh]

#26 #24 NOT #25

#27 #16 and #26

[CENTRAL (cochrane) Search Strategy]

#1 MeSH descriptor: [Low Back Pain] explode all trees

#2 MeSH descriptor: [Sciatica] explode all trees

#3 MeSH descriptor: [Radiculopathy] explode all trees

#4 (lumbar or lumbosacral or lumbo-sacral or back) near/5 (pain* or ache* or aching):ti,ab,kw (Word variations have been searched)

#5 backache* or lumbago or sciatica:ti,ab,kw (Word variations have been searched)

#6 radiculopathy or radiculitis or radicular pain*:ti,ab,kw (Word variations have been searched)

#7 (nerve root* near/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ti,ab,kw (Word variations have been searched)

#8 {or #6-#7}

#9 back* or lumbosacral or lumbo-sacral or lumbar:ti,ab,kw (Word variations have been searched)

#10 #8 and #9

#11 {or #1-#5, #10}

#12 MeSH descriptor: [Moxibustion] explode all trees

#13 MeSH descriptor: [Artemisia] explode all trees

#14 moxibustion or moxabustion or moxa or artemisia or mugwort$:ti,ab,kw (Word variations have been searched)

#15 {or #12-#14}

#16 #11 and #15

#17 (Select only trials)

[EMBASE Search Strategy]

#1 'Low Back Pain'/exp

#2 'Sciatica'/exp

#3 'Radiculopathy'/exp

#4 ((lumbar OR lumbosacral OR 'lumbo sacral' OR back) NEAR/5 (pain* OR ache* OR aching)):ab,ti

#5 (backache* or lumbago or sciatica):ab,ti

#6 (radiculopathy or radiculitis or radicular pain*):ab,ti

#7 (nerve root* NEAR/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ab,ti

#8 {or #6-#7}

#9 (back* or lumbosacral or lumbo-sacral or lumbar):ab,ti

#10 #8 and #9

#11 {or #1-#5, #10}

#12 Moxibustion/exp

#13 Artemisia/exp

#14 (moxibustion or moxabustion or moxa or artemisia or mugwort$):ab,ti

#15 {or #12-#14}

#16 #11 and #15

#17 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti

#18 #16 and #17

[Chinese database search strategy : CNKI, VIP, Wanfang]

#1 腰痛 and 灸

#2 坐骨神经痛 and 灸

#3 神经根型颈椎病 and 灸

#4 腰椎 and 灸

#5 腰骶部 and 灸

#6 背痛 and 灸

#7 神经根炎 and 灸

#8 神经根性疼痛 and 灸

#9 神经根 and 灸

#10 腰痛 and 艾

#11 坐骨神经痛 and 艾

#12 神经根型颈椎病 and 艾

#13 腰椎 and 艾

#14 腰骶部 and 艾

#15 背痛 and 艾

#16 神经根炎 and 艾

#17 神经根性疼痛 and 艾

#18 神经根 and 艾

#19 腰痛 and 蒿

#20 坐骨神经痛 and 蒿

#21 神经根型颈椎病 and 蒿

#22 腰椎 and 蒿

#23 腰骶部 and 蒿

#24 背痛 and 蒿

#25 神经根炎 and 蒿

#26 神经根性疼痛 and 蒿

#27 神经根 and 蒿

#28 or/#1-#27

PRISMA- P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		55
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		475-479
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			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		468-470
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		468-470
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		96-130

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		133-136
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		148-197
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		199-214
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	☐		199-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		222-240
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		223-229
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		231-240
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		231-240
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		176-197
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 study level, or both; state how this information will be used in data synthesis	☐		242-251
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		291-301
	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 (e.g., I^2, Kendall's tau)	☐		279-301

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		303-321
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		291-301
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		274-277
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		291-301

BMJ Open

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, moxibustion, systematic review, meta analysis, traditional medicine

Effectiveness and safety of moxibustion treatment for nonspecific lower back pain: protocol for a systematic review

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ABSTRACT

Introduction: Many patients experience acute lower back pain that becomes chronic pain. The proportion of patients using complementary and alternative medicine to treat lower back is increasing. Even though several moxibustion clinical trials for lower back pain have been conducted, the effectiveness and safety of moxibustion intervention is controversial. The Purpose of this study protocol for a systematic review is to evaluate the effectiveness and safety of moxibustion treatment for nonspecific lower back pain patients.

Methods and Analysis: We will conduct an electronic search of several databases from their inception to May 2017, including EMBASE, PubMed, Cochrane Central Register of Controlled Trial, Allied and Complementary Medicine Database, Wanfang Database, Chongqing VIP Chinese Science and Technology Periodical Database, China National Knowledge Infrastructure Database, Korean Medical Database, Korean Studies Information Service System, National Discovery for Science Leaders, Oriental Medicine Advanced Searching Integrated System, the Korea Institute of Science and Technology, and KoreaMed. Randomized controlled trials investigating any type of moxibustion treatment will be included. The primary outcome will be pain intensity and functional status/disability due to lower back pain. The secondary outcome will be a global measurement of recovery or improvement, work-related outcomes, radiographic improvement of structure, quality of life, and adverse events (presence or absence). Risk ratio or mean differences with a 95% confidence interval will be used to show the effect of moxibustion therapy when it is possible to conduct a meta-analysis.

Ethics and Dissemination: This review will be published in a peer-reviewed journal and will be presented at an international academic conference for dissemination. Our results will provide current evidence of the effectiveness and safety of moxibustion treatment in nonspecific lower back pain patients, and thus will be beneficial to patients, practitioners, and

policy makers.

Trial registration number: CRD42016047468 in PROSPERO 2016

Strengths and limitations of the present study protocol

- Our review provides a systematic, objective, and comprehensive evaluation of the effectiveness and safety of moxibustion treatment in patients with lower back pain that is nonspecific.
- Our review and meta-analysis provide new and useful information for practitioners, policymakers, and patients.
- Various treatments with moxibustion and clinical outcomes reviewed in our study will help to design clinical trial studies of moxibustion treatment for nonspecific lower back pain.
- Chinese and Korean databases will be searched to avoid a language bias.
- The major limitation of our study protocol is that some of the reviewed trials may have small sample sizes; this limitation affects our objective and comprehensive assessment of the risks and benefits of moxibustion treatment for nonspecific lower back pain.

INTRODUCTION

More than 70% of people suffer from lower back pain in developed countries[1]. Approximately 90% of back pain is nonspecific[2], indicating that most people the pathophysiological origin of the back pain cannot be specified[1]. Moreover, specifying and treating the factor that contributes to lower back pain is difficult because several co-related factors are involved, including psychological, work-related, and other individual factors[3]. Back pain is spontaneously relieved, but 5 ~ 20% of acute back pain patients suffer from chronic or persistent lower back pain[4–7]. The widely accepted definition of chronic lower back pain is a pain that persists for more than three months[8]. Even though conventional treatments such as medication or surgery have shown some efficacy against lower back pain[9,10], many lower back pain patients are dissatisfied with conventional treatment[11].

The proportion of patients using complementary and alternative medicine to treat lower back is increasing[12]. Acupuncture plays an important role in Traditional East Asian Medicine (TEAM) treatment of pain[13]. Several systematic reviews on the effectiveness and safety of acupuncture treatment in lower back pain patients have been published[14–17]. Moxibustion is an important treatment modality in TEAM treatment that stimulates acupoints with the heat energy of a burning herbal preparation[13,18]. Absorption of the therapeutically active components of the herbal preparation also contributes to the effect of moxibustion[18]. In TEAM theory, moxibustion treatment promotes qi stimulation and resolves qi stagnation at an acupoint[18]. Two types of moxibustion, direct moxibustion and indirect moxibustion, are widely used in TEAM treatment. Systematic reviews have been published about the effectiveness of moxibustion in several diseases, including insomnia, hypertension, irritable bowel syndrome, and constipation[19–22]. However, a systematic review that focuses especially on the effectiveness of moxibustion treatment in nonspecific lower back pain has not been published yet.

A systematic review summarizes the evidence of relevant current clinical trial studies; this effort provides supportive information for the design of future clinical trial studies. A systematic review of studies on the effectiveness of Traditional Chinese Medicine (TCM) treatment of back pain was published in 2015[1]. This review of TCM treatment for lower back pain deals with studies involving whole TCM interventions such as acupuncture, acupressure, moxibustion, cupping, Gua Sha, qigong, herbal medicine, and tuina treatments. However, the focus of that review was only pain intensity and disability measured with continuous outcome variables such as the visual analogue scale. There were no articles on moxibustion treatment for lower back pain included in the review; however, other parameters such as quality of life, work related outcome, side effects, and the proportion of responders are also important and valuable clinical outcome variables in patients with lower back pain. If we do not restrict outcome measures to only the intensity of pain and disability measured by continuous outcome variables, we can identify more moxibustion clinical trials and include Korean databases since moxibustion therapy is widely used in Korea for the treatment of lower back pain. The last search by the previous review was conducted in 2014; however, additional clinical trials have been conducted since. Thus, we could include and analyze more moxibustion clinical trials than did the previous review. And the range of interventions that are explored in that previous review is too broad to clarify the critical factors related to moxibustion treatment of lower back pain that are of interest to practitioners and researchers; such factors include the treatment duration, position, intensity, frequency, species of moxa, various outcome parameters, and side effects of moxibustion treatment. A systematic review of studies on the effectiveness of heat sensitive moxibustion treatment for a lumbar disc herniation has also been published[23]. However, as the prevalence of lower back pain that is secondary to a lumbar disc herniation (LDH) is low, it is not our target condition. Only 3 to 4 percent of patients with lower back pain who came to a primary clinic suffered from spinal

stenosis or a lumbar disc herniation[24]. L5 and S1 spinal nerve root damage due to disc protrusion or degenerative changes in the vertebrae are common causes of lower back pain in patients with a lumbar disc herniation[25]. Hence, nonspecific lower back pain and LDH have different pathophysiologies.

Our preliminary search on moxibustion treatment for lower back pain found several clinical studies with various experimental designs; for example, moxibustion versus usual care or conventional treatment, moxibustion versus another TCM intervention such as (electro) acupuncture, and moxibustion adjuvant therapy with acupuncture, among others. Thus, we believe that our study will overcome the limitations of previous systematic reviews of studies involving lower back pain and TCM [1,23].

To our knowledge, a systematic review that focuses on the effectiveness of various types of moxibustion treatment for nonspecific lower back pain and includes Chinese and Korean studies has not been published. Thus, we propose to conduct a systematic review that focuses on the effectiveness and safety of moxibustion treatment in patients with nonspecific lower back pain. We will summarize the current evidence and provide useful information to practitioners, patients, and policymakers. A summary of the current evidence from moxibustion clinical trial studies of lower back pain will benefit the development of future moxibustion clinical trial protocols. In the present article, we describe our methods and plan for a systematic review.

Objectives

The objective of the present review is to systematically evaluate the effectiveness and safety of moxibustion treatment compared to placebo control, conventional treatment, or no treatment in nonspecific lower back pain patients evaluated by pain intensity and functional

status/disability.

METHODS

Study registration

The systematic review protocol registration number in the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42016047468. This systematic review protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines[26,27]. In addition, our review will be conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[28].

Criteria for study inclusion

Type of studies

We will include only randomized controlled trials (RCT) in this review. Several Chinese trials do not provide detailed description of the randomization method used. We will include such studies if the authors have mentioned about the randomization method used (随机). However, we will grade these studies as high in the "risk of bias assessment" if detailed description on the randomization process is not provided. Furthermore, if an incorrect randomization method such as coin toss was used, the study will not be included.

Type of participants

Patients diagnosed with only nonspecific lower back pain will be included in the review. Trials studies of lower back pain due to other pathologies such as lumbar disc herniation, fibromyalgia, tumor, compression fracture, infection, trauma, cauda equine syndrome,

vertebral canal stenosis, scoliosis, or ankylosing spondylitis will be excluded. There will be no restriction of sex, age, ethnicity, disease duration, or disease severity.

Type of interventions

Moxibustion therapy will be compared to a placebo control, conventional treatment, no treatment, and an unproven control treatment. Moxibustion adjunctive therapy in combination with conventional treatment will be compared to conventional treatment alone. Any type of moxibustion will be included, regardless of the treatment frequency, duration, material, type, and method. Studies involving direct moxibustion, indirect moxibustion, warm needling, moxa-burner moxibustion, heat sensitive moxibustion, natural moxibustion, herbal patching, and crude drug moxibustion will also be included. Research that compares different moxibustion materials, doses, or durations of moxibustion treatment will not be included. Studies that evaluated the effect of moxibustion with at least 1 day of follow-up will be included.

Primary outcomes.

Pain intensity and functional status/disability will be a primary outcome. Chief complaints of nonspecific low back pain are pain and functional disability. Moreover, there are no objective biomarkers and parameters to evaluate lower back pain. Therefore, we selected pain intensity and functional status/disability as primary outcomes. These primary outcomes were also widely used in several of the previous systematic reviews on various interventions for lower back pain[1,29–33]. Other important outcomes used in these reviews were considered secondary outcomes of our review. Pain intensity will be evaluated using the visual analogue scale (VAS)[34] or the numerical rating scale (NRS)[35]. As VAS is

continuous data and NRS is dichotomous data, VAS and NRS will not be mixed in the meta-analysis. Functional status/disability will be evaluated using validated measurement tools such as the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability Scale[36,37].

Secondary outcome.

The secondary outcomes will include the following: 1) global measurements of recovery or improvement, such as subjective symptom improvement, the proportion of responders, overall improvement, and perceived recovery; 2) work-related outcomes, such as productivity, return to work status, and the number of absent days for work; 3) radiographic improvement of structure; 4) quality of life measurements using validated tools such as the Short Form Survey Instrument (SF-36) [38] and Euroqol-5D (EQ-5D) [39]; and 5) complications and adverse events

Search Methods

Electronic search

We will conduct an electronic search of several databases from their inception to May 2017. Four English databases will be searched, namely, EMBASE (OVID), MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Allied and Complementary Medicine Database (AMED); three Chinese database will be searched, namely, the Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and China National Knowledge Infrastructure Database (CNKI); and six Korean databases will be searched, namely, the Korean Medical Database (KMBASE), the Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), the Oriental Medicine Advanced Searching Integrated System

(OASIS), Korea Institute of Science and Technology (KISTI), and KoreaMed. The search term will be composed of two parts, moxibustion (e.g., moxibustion or moxabustion or moxa or artemisia or mugwort) and back pain (e.g., lower back pain, sciatica, radiculopathy, lumbago, backache, back pain, or lumbo-sacral). The online Supplementary Appendix 1 present our detailed search strategy that will be specific to MEDLINE (PubMed).

Searching other resources

PROSPERO, the International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov will also be searched to identify systematic reviews or ongoing/completed clinical trials. We will conduct a hand search of relevant journals and their conference proceeding. Thesis and bibliographic references of included trials will also be reviewed.

Analysis

Study selection

Two review authors (J Leem and Y Cho) will independently screen titles and abstracts in retrieved article lists from independent electronic and hand searches to exclude any obviously irrelevant articles. The full text of the remaining articles will be downloaded to assess their eligibility for inclusion in our review according to predefined criteria. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Data extraction and management

Two review authors (J Leem and Y Cho) will read all included articles and extract data according to a predefined data sheet that includes the publication year, author, title, journal, country, hospital setting, study design, allocation concealment, randomization method,

blinding, participants number, dropout number, intervention of treatment and control groups, treatment frequency and number, diagnostic criteria, disease duration, disease severity, outcome and results, and adverse event. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision. We will request via e-mail that the corresponding author of the original study send data when the results are ambiguous.

Assessment of reporting quality and risk of bias

Two review authors (J Leem and Y Cho) will independently assess the risk of bias according to the Cochrane risk of bias tool[40] outlined in the Cochrane Handbook for Systematic Reviews for Intervention[41]. Risk of bias assessment categories will include the following: (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other biases. The level of the risk of bias will be evaluated as either a low, high, or unclear risk of bias. Disagreement between these two authors will be resolved by discussion. If these authors do not reach an agreement, a third review author (D Nam) will make the final decision.

Unit of analysis

If studies measure the same outcome repeatedly, we will perform an analysis according to a timeline definition. Immediate follow-up will mean up to one week after the last intervention. Short-term follow-up will mean from one week to three months. Intermediate-term follow-up will mean from three months to 1 year after the last treatment. Long-term follow-up will mean more than 1 year after the last treatment. If two or more moxibustion treatment arm exist, the number of control group patients will be divided by the number of moxibustion

treatment groups and will be synthesized in a meta-analysis

Measures of a treatment effect

For dichotomous data, a risk ratio (RR) and the 95% confidence (CI) interval will be used to estimate a treatment effect. For continuous data, the mean difference (MD) and the 95% CI will be used to estimate a treatment effect when the same outcome scale or method is used. Standardized mean difference (SMD) and the 95% CI will be used to estimate a treatment effect when a different outcome scale or method is used.

Managing missing data

We will contact the corresponding author of an article via e-mail to obtain any missing data. If there is no response to an e-mail, we will exclude the data from our analysis, and describe the reason and impact of this exclusion in the Discussion section.

Assessment of a reporting bias

Publication bias will be assessed visually using funnel plot asymmetry if more than 10 articles are included[41]. An Egger's regression test will be used to quantitatively evaluate funnel plot asymmetry[42].

Assessment of heterogeneity

The heterogeneity of included studies will be quantitatively evaluated using an I^2 statistic that is derived from a chi-square test. The I^2 statistic will be interpreted according to the following criteria: 1) 75-100% will indicate considerable heterogeneity; 2) 50-90% will indicate substantial heterogeneity; 3) 30-60% will indicate moderate heterogeneity; 4) 0-40% will indicate little to no heterogeneity. In this manner, an I^2 statistic of more than 50% will

indicate the presence of substantial heterogeneity for the included studies[43]. If the I^2 statistic is more than 75%, a meta-analysis will not be conducted[44]. Instead, we will qualitatively describe the effectiveness and safety of moxibustion treatment. If the I^2 statistic belongs to both heterogeneity categories, we will use both adjectives. For example, if I^2 statistic is 55%, we will express the heterogeneity as "moderate to substantial heterogeneity."

Data synthesis and grading of quality of evidence

The Review manager (REVMAN) software for Windows will be used to perform a meta-analysis and to calculate the risk ratio or (standardized) mean difference (Version 5.3; Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will adopt a random effect model when the I^2 statistic is more than 50%, otherwise we will adopt a fixed effect model in a meta-analysis. If we are unable to conduct meta-analysis due to lack of clinical studies or heterogeneity, we will present the effect size and 95% confidence interval of every outcome in each clinical trial and describe the meaning of important results in the discussion section qualitatively. To summarize the findings of the meta-analysis and describe the strength of evidence, we will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach[41].

Subgroup analysis

To identify heterogeneity between the included studies, a subgroup analysis will be conducted if there is sufficient number of articles in each subgroup. The criteria of a subgroup analysis will be as follows: 1) disease duration, such as chronic (more than 3 months) or acute lower back pain (we will conduct a subgroup analysis according to disease duration even though there are not sufficient number of included studies); 2) type of control group, such as placebo moxibustion, conventional treatment, other TCM treatment, and no

treatment; 3) type of moxibustion, such as direct moxibustion, indirect moxibustion, warm needling moxibustion, moxa burner moxibustion, heat sensitive moxibustion, and crude drug moxibustion; 4) species of herb used in the moxibustion treatment; and 5) treatment number, frequency, and duration.

Sensitivity analysis

If there are a sufficient number of included articles, a sensitivity analysis will be carried out after removing low quality articles to identify the robustness of a result. The methodological quality will be assessed according to the "risk of bias" tool[40]. After excluding low quality articles that have more than three "risk of bias categories" graded as "high risk of bias," we will conduct a second meta-analysis. The results and effect size of the two meta-analyses will be compared and discussed.

DISCUSSION

The purpose of this proposed systematic review and meta-analysis will be to evaluate the effectiveness and safety of moxibustion treatment of nonspecific lower back pain. When compared to acupuncture research, the quantity and quality of moxibustion therapy research is relatively low. The STandards for Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM) was published in Chinese in 2013[45], but has not been widely adopted and translated into English. A recent systematic review was published on TCM treatment of lower back pain[1]. This review included a variety of interventions that are practiced in TCM, such as acupuncture, moxibustion, herbal medicine, cupping, and manual therapy, among others. However, the various interventions that were included in that review have too broad of a range to appropriately evaluate the issues that are specific to moxibustion treatment of lower back pain. Moreover, it did not include any trial studies of moxibustion treatment. A

systematic review has also been published regarding the effectiveness of heat sensitive moxibustion for lumbar disc herniation[23]. However, this review is not concerned with nonspecific back pain, but rather, lower back pain that is secondary to lumbar disc herniation. Therefore, the protocol described here is for the first systematic review and meta-analysis on the effectiveness and safety of any type of moxibustion treatment in nonspecific lower back pain patients. We anticipate that our review and meta-analysis will provide useful information to practitioners, policymakers, and patients.

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AUTHORS' CONTRIBUTIONS

Dongwoo Nam conceived of the study. The protocol was drafted by Jungtae Leem and Yeeun Cho. The search strategy was developed by Seunghoon Lee and Sanghoon Lee. The inclusion criteria were developed by Yeoncheol Parka and Byungkwan Seo. The authors Jungwon Kang and Eun-jung Kim revised the manuscript. The authors Yoonjae Lee, In-Hyuk Ha, and Hyun-jong Lee developed the analysis plan. Jungtae Leem submitted the manuscript for publication. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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Appendix 1 :

[MEDLINE(Pubmed) Search Strategy]

#1 Low Back Pain/

#2 Sciatica/

#3 Radiculopathy/

#4 (lumbar OR lumbosacral OR lumbo-sacral OR back) adj5 (pain* OR ache* OR aching) [TIAB]

#5 backache*[TIAB] OR lumbago[TIAB] OR sciatica[TIAB]

#6 radiculopathy[TIAB] OR radiculitis[TIAB] OR radicular pain*[TIAB]

#7 (nerve root* adj5 (pain* OR avulsion OR compress* OR disorder* OR pinch* OR inflam* OR imping* OR irritat* OR entrap* OR trap*)) [TIAB]

#8 {or #6-#7}

#9 back*[TIAB] OR lumbosacral[TIAB] OR lumbo-sacral[TIAB] OR lumbar[TIAB]

#10 #8 and #9

#11 {or #1-#5, #10}

#12 Moxibustion/

#13 Artemisia/

#14 (moxibustion or moxabustion or moxa or artemisia or mugwort$).tw.

#15 {or #12-#14}

#16 #11 and #15

#17 randomized controlled trial [PT]

#18 controlled clinical trial [PT]

#19 randomized [TIAB]

#20 placebo [TIAB]

#21 clinical trials as topic [mesh: noexp]

#22 randomly [TIAB]

#23 trial [TI]

#24 {or #17-#23}

#25 animals [mh] NOT humans [mh]

#26 #24 NOT #25

#27 #16 and #26

[CENTRAL (cochrane) Search Strategy]

#1 MeSH descriptor: [Low Back Pain] explode all trees

#2 MeSH descriptor: [Sciatica] explode all trees

#3 MeSH descriptor: [Radiculopathy] explode all trees

#4 (lumbar or lumbosacral or lumbo-sacral or back) near/5 (pain* or ache* or aching):ti,ab,kw (Word variations have been searched)

#5 backache* or lumbago or sciatica:ti,ab,kw (Word variations have been searched)

#6 radiculopathy or radiculitis or radicular pain*:ti,ab,kw (Word variations have been searched)

#7 (nerve root* near/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ti,ab,kw (Word variations have been searched)

#8 {or #6-#7}

#9 back* or lumbosacral or lumbo-sacral or lumbar:ti,ab,kw (Word variations have been searched)

#10 #8 and #9

#11 {or #1-#5, #10}

#12 MeSH descriptor: [Moxibustion] explode all trees

#13 MeSH descriptor: [Artemisia] explode all trees

#14 moxibustion or moxabustion or moxa or artemisia or mugwort$:ti,ab,kw (Word variations have been searched)

#15 {or #12-#14}

#16 #11 and #15

#17 (Select only trials)

[EMBASE Search Strategy]

#1 'Low Back Pain'/exp

#2 'Sciatica'/exp

#3 'Radiculopathy'/exp

#4 ((lumbar OR lumbosacral OR 'lumbo sacral' OR back) NEAR/5 (pain* OR ache* OR aching)):ab,ti

#5 (backache* or lumbago or sciatica):ab,ti

#6 (radiculopathy or radiculitis or radicular pain*):ab,ti

#7 (nerve root* NEAR/5 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)):ab,ti

#8 {or #6-#7}

#9 (back* or lumbosacral or lumbo-sacral or lumbar):ab,ti

#10 #8 and #9

#11 {or #1-#5, #10}

#12 Moxibustion/exp

#13 Artemisia/exp

#14 (moxibustion or moxabustion or moxa or artemisia or mugwort$):ab,ti

#15 {or #12-#14}

#16 #11 and #15

#17 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti

#18 #16 and #17

[Chinese database search strategy : CNKI, VIP, Wanfang]

#1 腰痛 and 灸

#2 坐骨神经痛 and 灸

#3 神经根型颈椎病 and 灸

#4 腰椎 and 灸

#5 腰骶部 and 灸

#6 背痛 and 灸

#7 神经根炎 and 灸

#8 神经根性疼痛 and 灸

#9 神经根 and 灸

#10 腰痛 and 艾

#11 坐骨神经痛 and 艾

#12 神经根型颈椎病 and 艾

#13 腰椎 and 艾

#14 腰骶部 and 艾

#15 背痛 and 艾

#16 神经根炎 and 艾

#17 神经根性疼痛 and 艾

#18 神经根 and 艾

#19 腰痛 and 蒿

#20 坐骨神经痛 and 蒿

#21 神经根型颈椎病 and 蒿

#22 腰椎 and 蒿

#23 腰骶部 and 蒿

#24 背痛 and 蒿

#25 神经根炎 and 蒿

#26 神经根性疼痛 and 蒿

#27 神经根 and 蒿

#28 or/#1-#27

PRISMA- P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not update for previous review
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		55
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		5-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		475-479
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			Not amendment for previous review
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		468-470
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		468-470
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			No roles exist
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		96-130

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐		133-136
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		148-197
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		199-214
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	☐		199-214
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		222-240
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		223-229
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		231-240
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		231-240
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		176-197
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 study level, or both; state how this information will be used in data synthesis	☐		242-251
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		291-301
	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 (e.g., I^2, Kendall's tau)	☐		279-301

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐		303-321
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		291-301
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		274-277
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		291-301