

INPLASY PROTOCOL

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Effect of moxibustion on inflammatory cytokines in patients with low back pain: a systematic review, meta-analysis, and meta-regression

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None declared.

Review question / Objective: To review the effectiveness of moxibustion on inflammatory cytokines in patients with low back pain.

Information sources: A search of several databases will be conducted, including the China National Knowledge Infrastructure (CNKI), Wanfang database, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, PubMed, and Web of Science. OpenDissertations (biblioboard.com/opendissertations/) will be searched to identify grey literatures to help to minimize publication bias. In addition, a manual search of related reviews and studies' reference lists will also be conducted.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2022 and was last updated on 26 August 2022 (registration number INPLASY202280100).

INTRODUCTION

Review question / Objective: To review the effectiveness of moxibustion on inflammatory cytokines in patients with low back pain.

Condition being studied: Low back pain (LBP) is a common problem worldwide.

People with LBP often complain of varying degrees of pain and disability. The leading cause of LBP is intervertebral disc degeneration (IDD). The pathological features of IDD involve many links, which include the production of pro-inflammatory mediators. Furthermore, recent evidence supports that pro-inflammatory cytokines and anti-inflammatory cytokines also play

an important part in the transition from acute pain to chronic pain. Therefore, inflammatory responses, which are induced by inflammatory cytokine overexpression, are considered to be critical events during LBP. To date, many pharmacological therapies have been widely used to treat LBP, but the side effects of Western medicine (e.g., non-steroidal anti-inflammatory drugs, steroids, opioids) are common in clinic. Therefore, alternative therapy without side effect is gradually becoming a trend to treat LBP. Moxibustion therapy is a branch of traditional Chinese medicine. In China and Japan, it has been widely used to treat LBP. Previous studies found that moxibustion was effective to relieve pain and dysfunction in LBP. However, the mechanism of moxibustion to treat LBP remains unclear. Inflammatory response is important in the progression and prognosis of LBP. Therefore, it deserves our exploration to analyze whether moxibustion can treat LBP by regulating inflammatory response. Inflammatory responses are induced by inflammatory cytokine overexpression. Several studies showed that patients treated with moxibustion had lower levels of proinflammatory cytokines than those in the control group. But there is a lack of systematic review to summarize the evidence of moxibustion on inflammatory cytokines in patients with LBP. Thus, the purpose of this study is to systematically assess and meta-analyze the efficacy of moxibustion on inflammatory cytokines in patients with LBP from randomized controlled trials (RCTs).

METHODS

Search strategy: We will identify RCTs from an electronic search of several databases (up to 31 March 2022): China National Knowledge Infrastructure (CNKI), Wanfang database, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, PubMed, and Web of Science. There were no restrictions on language or publication date. Additionally, OpenDissertations (biblioboard.com/ opendissertations/) will be searched to identify grey literatures to help to minimize

publication bias. A manual search of related reviews and studies' reference lists will also be conducted. The search terms format, guided by the PICO (P-participant; I-intervention; C-comparison; O-outcome) framework, included keywords, terms, and Medical Subject Headings (Mesh) related to moxibustion (Intervention); inflammatory cytokines (Outcome); and LBP (Participants). The search process was conducted by two independent reviewers.

Participant or population: This systematic review focus on patients with LBP. Disorders that lead to LBP, such as lumbar disc herniation (LDH), intervertebral disc degeneration (IDD), spinal stenosis, sciatica, ankylosing spondylitis, failed back surgery syndrome, will also be included.

Intervention: This systematic review focus on moxibustion therapy. As a complementary medicine, moxibustion is a technique that involves the burning of mugwort (moxa, *Artemisia argyi*) to facilitate healing over specific acupuncture points.

Comparator: There is no restriction on interventions in the control group.

Study designs to be included: Randomized controlled trials (RCTs) focused on human trials will be included.

Eligibility criteria: We will only include RCTs that examined the effectiveness of moxibustion intervention in adults with acute, subacute or chronic low back pain. Additionally, we will include studies if the observed differences were thought to be due to the unique contribution of moxibustion, which may include studies in which moxibustion was delivered as part of a package of intervention—that is, if the effects moxibustion could be isolated; for example, studies comparing moxibustion plus acupuncture with acupuncture alone would be included, whereas studies comparing moxibustion plus acupuncture with moxibustion alone would not. The primary outcomes considered are inflammatory cytokines, including TNF- α , interferon (IFN-) α , IFN- γ , IL-1 β , IL-2, IL-4,

IL-6, IL-10, IL-17. The secondary outcome is incidence rate of adverse events related to moxibustion intervention. We will exclude studies that LBP is caused by tumor or infection. We will also exclude studies if moxibustion was combined with other therapies, making it difficult to distinguish the effect of moxibustion; for example, a study comparing moxibustion plus acupuncture with another type of treatment (e.g., Chinese herbal medicine). Studies comparing effectiveness of different types of moxibustion will also be excluded (e.g., heat-sensitive moxibustion vs. manual moxibustion).

Information sources: A search of several databases will be conducted, including the China National Knowledge Infrastructure (CNKI), Wanfang database, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, PubMed, and Web of Science. OpenDissertations (biblioboard.com/ opendissertations/) will be searched to identify grey literatures to help to minimize publication bias. In addition, a manual search of related reviews and studies' reference lists will also be conducted.

Main outcome(s): The primary outcomes considered are inflammatory cytokines, including tumor necrosis factor (TNF-) α , interferon (IFN-) α , IFN- γ , interleukin (IL-) 1β , IL-2, IL-4, IL-6, IL-10, IL-17.

Additional outcome(s): The secondary outcome is the incidence rate of adverse events related to moxibustion intervention.

Data management: All the records retrieved from the databases will be first exported to EndNote X9 for removing of duplication. First, title and abstracts of the records will be screened by two independent reviewers for eligibility, in the absence of an abstract, records will be retained for full text review. Second, the same reviewers will assess the full text of potential studies to determine ultimate inclusion in the review. Finally, in case of any disagreement, a decision will be made by consensus with a senior researcher.

Quality assessment / Risk of bias analysis:

Two independent reviewers will assess risk of bias (RoB) according to the guidelines of the Cochrane Back Review Group. The RoB assessment has 13 independent criteria; with a judgement of 'yes', 'unclear', or 'no'. The overall RoB for each study will be assessed as follows: low RoB if none of the criteria was assessed as 'no' and three or less were assessed as 'unclear'; moderate if one was assessed as 'no' or none was assessed as 'no' but four or more were assessed as 'unclear', and all other cases will be assumed to pertain to high RoB. Disagreements between the two reviewers on RoB will be resolved by consensus.

Strategy of data synthesis: We will perform meta-analyses of clinically homogenous studies (participants, treatment procedure, control group, timing of follow-up, and outcomes) to provide estimates of the efficacy of moxibustion for inflammatory cytokines. If we could not combine data, we will present a narrative synthesis of results. Review Manager (RevMan) (V.5.3) will be used to carry out meta-analysis. A fixed-effect or random-effects model (depending on the level of clinical and methodological heterogeneity) will be used for pooled results. We consider a P value of 0.05 or less to be statistically significant. We plan to express results as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes and (unstandardized) mean difference (MD) with 95% CI for continuous outcomes if the same measurement tool was used to measure the same outcome across separate studies. Alternatively, we will summarize continuous outcomes using the standardized mean difference (SMD) when studies measure the same outcome but employ different measurement tools.

Subgroup analysis: We plan to conduct subgroup analyses according to the nature of the control interventions, since these factors may cause variations in outcomes. When at least 10 studies reported data of the same variable, meta-regression will be conducted to investigate the potential sources of heterogeneity. The possible covariates that could explain the

heterogeneity include publication year, geographical region, method of randomization, conditions of participants, types of moxibustion, types of control groups, and frequency of intervention.

Sensitivity analysis: A leave-one-out sensitivity analysis will be used to explore the robustness of the intervention effect if sufficient data were available.

Language restriction: There is no restriction on publication language.

Country(ies) involved: China.

Keywords: Low back pain; moxibustion; meta-analysis; systematic review.

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