SYSTEMATIC REVIEW AND META-ANALYSIS

Moxibustion Treatment for Knee Osteoarthritis
A Systematic Review and Meta-Analysis

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Abstract: To determine whether the administration of moxibustion is an effective treatment for knee osteoarthritis (KOA).

We conducted a search of relevant articles using Medline, EMBASE, the Web of Science, and the Cochrane Library published before October 2015. The Western Ontario and McMaster Universities’ Osteoarthritis Index (WOMAC scale) and the short form 36 questionnaire (SF-36 scale) were assessed. Evidence grading was evaluated according to the Grading of Recommendations, Assessment, Development, and Evaluation system.

Four studies containing 746 participants fulfilled the inclusion criteria in the final analysis. In terms of quality of life (QOL), the meta-analysis of 2 randomized clinical trials (RCTs) showed significantly effects of moxibustion only in bodily pain (BP) compared with those in the control group (n = 348; weighted mean difference [WMD], 4.36; 95% confidence intervals [CIs], 2.27–6.44; P < 0.0001; heterogeneity: χ² = 1.53, I² = 22%; F1 = 34%) in all of the subcategories of the SF-36 scale, with moderate quality. The meta-analysis of the 2 included trials showed that there was not a statistically significant difference in the pain or function subscale for the WOMAC scale when the 2 groups were compared (n = 322; WMD, 17.63; 95% CI, −23.15–58.41; P = 0.40; heterogeneity: χ² = 19.42, P < 0.0001, I² = 95%), with low or moderate quality separately.

The administration of moxibustion can to some extent alleviate the symptoms of KOA. More rigorous, randomized controlled trials are required in the future.

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Abbreviations: AE = adverse event, BP = bodily pain, CI = confidence interval, GH = general health, HSM = heat-sensitive moxibustion, KOA = knee osteoarthritis, PF = physical functioning, QOL = quality of life, SF = social role functioning, SF-36 scale = short form 36 questionnaire, UC = usual care, VT = vitality, WMD = weighted mean difference, WOMAC scale = Western Ontario and McMaster Universities’ Osteoarthritis Index.

INTRODUCTION

Knee osteoarthritis (KOA), known as severe degenerative arthritis, is common in middle-aged and elderly people. It causes pain and dysfunction that greatly reduce the patients’ quality of life (QOL).1 An earlier study demonstrated that Chinese people more than 60 years of ages hared a high incidence (19.4%) of doctor-diagnosed and symptomatic KOA.2 This number is expected to rise in the future because of increases in the obese population and in life expectancy.3 However, the nonsurgical treatment of KOA has not changed in recent decades, and the symptomatic treatment based on pharmacological therapy was still the prevalent as well as the preferred mode of treatment.4 Unsurprisingly, a prolonged therapy with medication would lead to undesired side effects, such as renal and hepatic toxicity, gastrointestinal bleeding, and ulcers.5

Moxibustion is a traditional oriental medicine that stimulates acupuncture points through heat generated by a flaming moxa wool, the herb artemisia vulgaris. It has frequently been recommended to treat a variety of illnesses as an adjuvant therapy, with or without acupuncture, such as malposition, colitis, muscle strain, urinary incontinence, soft-tissue injury, postlaminectomy pain, asthma, reactive arthritis, fibromyalgia, and conditions related to aging.6 KOA is the 3rd common indication.7,8 Moxibustion is widely utilized for the treatment of KOA in Asian countries.9 Currently, moxibustion treatments can be categorized as traditional moxibustion, drug moxibustion, and modern moxibustion.10 The present meta-analysis focused on traditional moxibustion, including both its direct or indirect application (i.e., whether there is contact with the skin). Currently, there are many animal experiments and reports about the clinical positive efficacy of moxibustion for the treatment of arthritis and pain;11 however, there is no rigorous evidence supporting this conclusion. The aim of the present meta-analysis was to evaluate the efficacy and safety of moxibustion in the management of patients with KOA.

METHODS

Literature Search

We searched the following electronic databases: Medline, EMBASE, the Web of Science, and the Cochrane Library. The search language was restricted to English. The search strategy was based on a combination of 2 concepts adjusted to each database. Concept 1 included all of the terms for KOA, and concept 2 included the terms for moxibustion. The Boolean operator AND was used to link the 2 concepts. The bibliographies of the included studies and dissertations were searched for additional publications. Additionally, relevant journals as well as files were manually searched and thoroughly read; we only accepted 1 set of data on the same topic in the event of multiple publication bias. All of the eligible studies were identified by
2 independent authors (AL, ZJW), and any disagreements were settled by consensus or consultation with a 3rd author (BL).

**Study Selection**

We included these studies into the meta-analysis if they fulfilled all of the following inclusion criteria: trials written in English had to be properly randomized; moxibustion was used as the sole intervention measure or was combined with another standard treatment for KOA, such as conventional medication or physiotherapy; and both groups can received the same foundation therapy. The exclusion criteria were as follows: the evaluation of the efficacy of moxibustion was absent in the studies; there was crossover in principle between the intervention in the control groups and moxibustion; the study was related to the comparison of the 2 types of moxibustion; and case reports, editorials, experimental studies, conference articles, non-English studies, and other studies that failed to provide detailed results were excluded.

**Quality Assessment**

Cochrane collaboration tool for assessing risk of bias was used to evaluate the methodological quality of the included trials. This tool focuses on the internal validity of the trial and assessment of risk of possible bias in different phases of the trial. The details are as follows: random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other bias. Each item was classified according to a high, low, or unclear risk of bias that is represented as high (H), low (L), and unclear (U), respectively. All of the assessments were conducted by 2 independent reviewers (AL, XG). Any controversies were settled by consensus or discussion with a 3rd author (BL).

**Data Extraction**

The relevant data from the eligible papers were double extracted by 2 authors (AL, YL) according to a predefined standardized protocol. Pertinent details included: author information, year, sample size, country, diagnostic criteria, patient’s age, outcome measures, intervention, and control regimen. Any discrepancies were resolved by consensus. When inadequate information existed in the studies, contacting the 1st authors to obtain and clarify the relevant data were essential as specified by the standardized protocol.

**Outcome Assessment**

The Western Ontario and McMaster Universities’ Osteoarthritis Index (WOMAC scale) and the short form 36 questionnaire (SF-36 scale) expressed as the standardized mean difference were used to analyze the summary estimates. The WOMAC scale, which includes ratings of pain, stiffness, and function, was used to evaluate the disability level of the patients with KOA. The SF-36 scale was used to assess the patients’ QOL and it covers 8 dimensions: physical functioning (PF), physical role functioning, bodily pain (BP), general health (GH), vitality (VT), social role functionality (SF), emotional role functionality (RE), and mental health.

**Statistical Analysis**

The Review Manager Software Package (RevMan Version 5.2, The Cochrane Collaboration, Copenhagen, 2014) was used to generate forest plots. The overall effect of moxibustion treatment was calculated as the weighted average of the inverse variance adjusted individual effects and 95% confidence intervals (95% CIs). The statistical heterogeneity among the individual studies was evaluated based on Cochrane Q test and the I² index, and the statistical heterogeneity was confirmed if I² was >75% and P < 0.10. A variance-based fixed effect model was applied to calculate the pooled effect; otherwise, a random effect model was used in the presence of statistically significant heterogeneity. If appropriate, the heterogeneity was identified and explained using a subgroup analysis. Evidence grading was evaluated according to the Grading of Recommendations, Assessment, Development, and Evaluation system.

**Ethical Statement**

As all analyses were grounded on previously published studies, ethical approval was not necessary.

**RESULTS**

**Search Results**

The initial literature search yielded a total of 185 articles. After duplicate checking and title and abstract screening, 30 publications met the inclusion criteria, and the full text of all 30 articles was available. Among these articles, 3 articles were excluded because intervention was not the sole moxibustion but was combined with acupuncture or medication; 4 articles were excluded because of a comparison of heat-sensitive moxibustion (HSM) and conventional moxibustion in the treatment of KOA; 2 articles were excluded because they were study protocols; and 17 articles were excluded because they were not written in English. Moreover, a manual search of relevant references did not identify additional studies. Finally, 4 intermediate- to high-quality studies were eligible for inclusion in the present meta-analysis (Figure 1).

**Participants and Study Characteristics**

Table 1 shows the characteristics of the eligible trials. Of the 4 citations included, a total of 746 participants (370 moxibustion, 376 control) divided into 8 groups (4 moxibustion, 4 control) were recruited in the final analysis. All of the studies were multi-center trials. Overall, 3 trials were performed in China, and 1 was performed in Korea. The moxibustion treatments in 3 randomized clinical trials (RCTs) were based on the traditional Chinese medicine theory as the guide for the implementation procedures. The points were chosen according to the traditional Korean medicine in the other RCT. Assessing the expectation regarding the effectiveness of moxibustion on KOA was conducted in 1 RCT. The patients in the studies were middle-aged and elderly; the average age ranged from 38 to 70 years. The mean duration of follow-up ranged from 3 to 28 weeks. The intervention types in the control groups were sham moxibustion in 2 studies, intraarticular sodium hyaluronate in 1 study, and usual care (UC) in 1 study. One RCT tested the positive effects of moxibustion on KOA, utilizing the following 3 randomized groups: HSM group, conventional moxibustion group, and intraarticular sodium hyaluronate control group. The HSM group was removed from this meta-analysis. KOA in patients retrieved from the articles was confirmed according to the American College of Rheumatology criteria in 3 trials and the criteria of the Guiding Principles of Clinical Research on New Drugs were used to diagnosis KOA in 1 study. Two RCTs calculated the appropriate sample
capacity before conducting the trials according to the previous pilot study. Three RCTs reported ethical approval of the study protocol from their Institutional Review Boards before the study enrollment of the 1st participant.

**Risk of Bias Assessment**

Based on the Cochrane Collaboration recommendation, 4 RCTs adopted allocation concealments, and comprehensive methodological processes and random sequence generation were reported. Assessor blinding was determined to be at a low risk of bias in all of the included studies. The participants and personnel were blinded in 2 trials; 1 RCT conducted an assessment of blinding effectiveness. Sufficient details of withdrawals and dropouts were described in all 4 studies. Two studies used the intention-to-treat approach in the data handling. One RCT reported the remedy for dropout. In the majority of the studies, whether enrollment of the participants was actually consecutive or not was unclear, so a selection bias could be completely excluded. The details of risk of bias are illustrated in Supplemental Figure 1, http://links.lww.com/MD/A881.

**Adverse Events**

Four RCTs reported relevant adverse events (AEs) in the active moxibustion group but only 1 AE in the control group; 1 study demonstrated that no AEs occurred in the study period. Otherwise, 3 RCTs noted region adverse reactions, for example, blisters, burn wounds, and skin flushing in local lesions. Two studies reported systemic AEs; however, only 1 reported positive symptoms, that is, pruritus and fatigue. Furthermore, 1 RCT assessed the severity of each AE according to Spilker AE classification and reported a high incidence (47%) of abnormal reactions, the majority of which were second-degree burns.

**WOMAC in Patients With Moxibustion and Non-Moxibustion**

In total, 2 studies reported the WOMAC scores in patients with moxibustion. The control group was sham-moxibustion or UC separately. A considerable statistical heterogeneity existed in the pain scores between the 2 studies ($\chi^2 = 19.42$, $P < 0.0001$, $I^2 = 95\%$), and the fixed-effects model was applied for performing the data analysis. Otherwise, the meta-analysis of the 2 eligible trials showed that there was not a statistically significant difference in the pain scores ($n = 322$; weighted mean difference [WMD], 17.63; 95% CI $-23.15$ to $58.41$; $P = 0.40$), although the participants with moxibustion statistically achieved a significantly greater improvement in the pain symptoms of WOMAC scale compared with the control groups in each study. With respect to the function score, which was similar to the pain score, the meta-analysis demonstrated that the function score in patients with moxibustion was not significantly lower, and it had a high heterogeneity ($n = 322$; WMD, 13.45; 95% CI $-26.99$ to $53.89$; $P = 0.51$; heterogeneity: $\chi^2 = 9.34$, $P = 0.002$, $I^2 = 89\%$) (Figure 2).
| Study, year | Country | Diagnostic Criteria | Participants | Intervention | Control | Outcome |
|-------------|---------|---------------------|--------------|--------------|---------|---------|
| Zhao et al\textsuperscript{20} (2014) | China | ACR | 110 Men and women with KOA assigned to either moxa group (n = 55, age: x ± SD = 65.80 ± 7.45 years) or control group (n = 55, age: X ± SD = 64.55 ± 8.38 years) | Moxa (1 session = 20 minutes, once daily, 3 times/week, total 6 weeks, acupoints: ST35, EX-LE 4, Ashi) | Sham moxa (same with moxa in regimen) | WOMAC scale |
| Ren et al\textsuperscript{21} (2015) | China | ACR | 136 Men and women with KOA assigned to either moxa group (n = 69, age: x ± SD = 65.61 ± 7.42 years) or control group (n = 67, age: X ± SD = 64.06 ± 8.65 years) | Moxa (1 session = 20 minutes, once daily, 3 times/week, total 6 weeks, acupoints: ST35, EX-LE4, Ashi) | Sham moxa (same with moxa in regimen) | SF-36 scale |
| Kim et al\textsuperscript{23} (2014) | Korea | ACR | 212 Men and women with KOA assigned to either moxa group (n = 102 age: median [25%–75% IQR] = 56 [52–62] years) or control group (n = 110 age, median [25%–75% IQR] = 57 [51–62] years) | Moxa (1 session = n.r., once daily, 3 times/week, total 4 weeks, acupoints: ST36, ST35, ST34, SP9, EX-LE04, SP10, Ashi) | UC (regimen performed according to own intention) | K-WOMAC scale |
| Chen et al\textsuperscript{22} (2015) | China | Guiding principles of clinical research on new drugs of traditional Chinese medicine | 288 Men and women with KOA assigned to either moxa group (n = 144, age, X ± SD = 53 ± 5.2 years) or control group (n = 144, age, x ± SD = 56 ± 5.0 years) | Moxa (1 session = 45 minutes, total 35 sessions for 30 days, acupoints: EX-LE5, EX-LE2) | Drug therapy (intraarticular: hyaluronate, sodium, 2 mL, 1/6d, total 5 times) | GPCRND-KOA scale knee circumference |

ACR = American College of Rheumatology, BDI = Beck Depression Inventory, GPCRND-KOA = guiding principle of clinical research on new drugs in the treatment of knee osteoarthritis score, IQR = interquartile range, K-WOMAC = Korean version of Western Ontario and McMaster Universities Questionnaire, NRS = numeric rating scale, SD = standard deviation, SF-36v2 = Short-Form 36 Health Survey.
FIGURE 2. Forest Plot for Some Outcomes.
SF-36 in Patients With Moxibustion and Non-Moxibustion

Two studies21,23 assessed the QOL in patients with KOA using the SF-36 scale. The control group was sham-moxibustion or UC separately. One RCT21 revealed that the participants with moxibustion experienced a considerably significant improvement in a GH score than the control group at week 6 \( (P = 0.015) \) and week 12 \( (P = 0.029) \); the same result applied to the VT score at week 12 \( (P = 0.042) \). The other study25 reported that the BP score, PF score, or SF score in the patients with moxibustion were separately higher than those scores of the patients in the control group \( (P = 0.0003) \) at week 5, 13; \( P = 0.0025 \) at week 5; and \( P = 0.0418 \) at week 5). The data in all of the subcategories of the SF-36 scale were quantitatively synthesized in the meta-analysis. The results showed that the BP score in the patients with moxibustion was significantly higher than that in the controls \( (n = 348); \) WMD, 4.36; 95% CI, 2.27–6.44; \( P < 0.0001 \); heterogeneity: \( \chi^2 = 1.53, P = 0.22, I^2 = 34\% \). However, no difference was detected with respect to the other domains in the intergroups. PF (WMD, 0.98; 95% CI, −0.97–2.93; \( P = 0.32 \)); mental health (WMD, −0.03; 95% CI, −2.50–2.45; \( P = 0.98 \)); emotional role functionality (WMD, 1.58; 95% CI, −4.70–1.53; \( P = 0.30 \)); physical role functioning (WMD, 1.13; 95% CI, −1.41–3.68; \( P = 0.38 \)); SF (WMD, 0.61; 95% CI, −1.50–2.72; \( P = 0.57 \)); VT (WMD, 2.92; 95% CI, 0.32–5.51; \( P = 0.03 \)), and GH (WMD, 2.57; 95% CI, −2.44–7.59; \( P = 0.31 \)). The data regarding the other 4 items are listed in Supplemental Figure 2, http://links.lww.com/MD/A881.

Evidence Grading

Evidence grading was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation system19 (Supplemental Table, http://links.lww.com/MD/A881). Ten outcomes in the WOMAC scale or SF-36 scale were analyzed in this meta-analysis. The level of evidence was moderate for 8 aspects in the SF-36 scale. For the WOMAC scale, the level of evidence was low for the pain score and moderate for the function score.}

DISCUSSION

Overall, many clinical trials have tested the efficacy of moxibustion in the treatment of KOA.5,25,26 In fact, the results of this meta-analysis supported, to some extent, the above suggestion. However, because of the small number of trials, low consistency, and standardization of the control intervention as well as the potential bias in the existing studies, we decided not to determine the practical availability of the management of KOA due a lack of sufficient supporting evidence.

To date, there have been 3 related systematic reviews about moxibustion regarding health supervision for KOA,2,27,28 all of which have clarified that moxibustion was significantly beneficial to relieving pain and improving function for patients with KOA. However, nearly all of the trials regarding KOA included in the above systematic reviews had a high risk of bias and low methodological quality. The purpose of this paper was to evaluate the effects of moxibustion on symptom management for patients with KOA by not only adding new clinical trials but also simultaneously improving the research quality of the studies. All of the studies included were characteristic of multicenter, randomized controlled trials, which guaranteed its external validity. An appropriate randomization sequence was generated in all of the trials included in this present analysis. Inadequate sequence generation in randomization studies tended to yield exaggerated treatment effects.29

Additionally, some RCTs22,23 included here employed various core outcome domains, such as functional performance tests (6-minute walk test); some objective and disease-specific parameters (knee circumference) quantify the results rather than simply evaluate the patients’ ratings of improvement and pain intensity used in other literature.30 To date, the SF-36 scale is the most widely used QOL measure in patients with health-related conditions.31 Initially developed in 1982, the WOMAC scale targeted patients with knee and hip osteoarthritis and has been validated in >80 language translations.14 The patient’s change in pain-related experience might be more incisively shown by the WOMAC pain subscale and the SF-36 BP scale, because it was reported that the pain-numerating scale was too superficial and simple to evaluate the complexity of a patient’s pain experience.31

As no significant difference existed in between groups (Guiding Principles of Clinical Research on New Drugs-KOA scores, \( P = 0.130 \); knee circumference, \( P = 0.141 \)), sodium hyaluronate intraarticular injection as a conventional treatment for KOA had been validated and widely acknowledged by the general,32 which indirectly identified that moxibustion played an important role in alleviating the symptoms in adults with KOA. Likewise, UC is the same as the above mentioned,33 but it is more straightforward because of a moderate effect size observed at 5 weeks (WOMAC score, \( P = 0.0477 \)) and 13 weeks (WOMAC score, \( P = 0.0518 \)) between groups. Additionally, each component of UC was based on previous evidence of benefits in the treatment management of KOA.34 In another study,27 no significant difference existed in the outcomes between conventional moxibustion with conventional medication groups in patients with KOA at each time point, indicating the effect of moxibustion in KOA.

At present, the AEs announced in the published literature concerning moxibustion therapy primarily involve burns, allergies, infections, nausea, loose lower eyelids, ectropion, death, and so on.6,27 However, the issue of whether moxibustion-induced burns are, in fact, an AE is still controversial.27 In Chinese traditional moxibustion, also known as scarring moxibustion, local minor burns, scarring, and purulence during treatment were taken for granted because many of the components take effect after entering the human body through burn-damaged skin.25,35 Additionally, in term of burns, some patients accepted these scars as the natural conclusion of moxibustion therapy. When weighing the pros and cons, it was reported that the appropriate distance for indirect moxibustion seems to be 3 to 4 cm.36,37 Furthermore, how much causal association between some AEs and moxibustion is still unclear. Certain factors, such as the duration, position, distance between moxa sticks and skin, the patient’s conditions, physicians’ proficiency, simulations from smoke, and even the treatment environment, and so on, can affect the safety of moxibustion.38

If the efficacy of moxibustion as a treatment for KOA is acknowledged, the underlying mechanism would draw much attention. Interests in research regarding the underlying mechanisms of moxibustion have grown in recent decades.39,40 Currently, the therapeutic effects of moxibustion are generally believed to be derived from radiation effects, thermal effects, and the pharmacological actions of moxa combustion.41 The ingredients of moxa smoke are complex, consisting of terpene compounds, aliphatic hydrocarbons, alcohols, aromatic hydrocarbons, and their oxides.25,42 Nevertheless, the exhaustive
understanding of the mechanisms of moxibustion therapy is still limited. It was previously reported that the sensation of heat as the foundation of moxibustion treatment is important. According to the traditional Chinese medicine theory, moxibustion is analogous to acupuncture in principle. Although it is more superficial, its effect on the sensory nerves is well known as “Zhen Jiu” in ancient China, and a mass of Chinese literatures or systematic reviews reported heat’s responsibility for symptom management in KOA. The synergistic effects of heat derived from moxibustion on the stimulation of some specific acupoints might be alike mechanism. Today, the primary speculation about moxibustion is that it acts through the local or system neural network and releases some neurotransmitters, such as opioidergics, beta endorphins, and adenosine triphosphate. Moreover, it was reported that moxibustion could modulate the inflammatory reactions through the degranulation of local mastocytes and activation of thermoreceptors and further normalize the immune system in a KOA rat model. Many studies have revealed that moxibustion could ease the nociceptive painful reception and improve the force of a rat’s limb tread through the regulatory mechanism of some signaling molecules, transcription factors, and even some mRNA, such as nitric oxide, signal transducer and activator of transcription 1, suppressor of cytokine signaling, c-Fos, transforming growth factor-β, insulin-like growth factor-I, and neuronal nitric oxide synthase. It was reported that the toll-like receptor-4 – myeloid differentiation factor 88 – nuclear factor kappa B signal transduction pathway was related to the changes in the knee-joint synovial tissue in rats with rheumatic arthritis. However, so far, all of these theories are little more than speculation.

Given the special feature of KOA, an active control was required to relieve the patient’s condition, and it was impossible to blind acupuncturists to the treatment because of the nature of the intervention. The sham moxibustion device, which is essential for differentiating the specific from the non-specific treatment effects, did produce heat but to a lesser extent than that of the true application. Although the sham device resembles the real one in appearance, and the reliability was previously examined and validated by Zhao et al., controversies still existed and there was some doubt regarding the availability of a double-blinded, randomized controlled trial in moxibustion research. Kim et al. reported a sham moxibustion device that was conditioned as much as possible to the minimum temperature; however, it could reach a heat level of 39°C. However, some physiological effect caused by this lower temperature of heat cannot be precluded. Additionally, compared with the verum, the nonspecific effects of the sham moxibustion might come from preventing heat stimulation on acupoints or affecting other areas beyond the acupuncture points. Moreover, moxibustion is primarily used only in the eastern countries but not in Europe, and the patients possess high expectations in these other areas. As moxibustion can bring about such positive placebo effects, the consequence of moxibustion plus a standard treatment in comparison to only the administration of a standard treatment is most likely to be a significant positive result. Hence, to realize that the patients were blinded, 2 RCTs recruited the patients who were naive to moxibustion and had never received moxibustion therapy until the study began, which might lead to a selection bias.

The limitations of this systematic review involve restrictions on the publication language, uniformity of the control group or moxibustion program and a small number of included RCTs. Some literatures or guidelines have well documented the distorting effects of location bias and publication bias on the systematic reviews and meta-analyses. In the present review, the retrieval language limited to English would generate a sampling bias, and because the majority of the trials are from China, some potential uncertainty concerning positive evidence for moxibustion might, to some extent, exist. Moreover, moxibustion is applied in clinical practice together with a high heterogeneity in the stimulating process, original materials, duration, frequency, selection of acupoints, etc. The empirical evidence from previous research has suggested that the therapeutic effect of moxibustion depends on the following 3 key factors: dose, location, and sensation. The effects of moxibustion may vary across any change in each factor. The high-level evidence requires wide strictness and consistency to support.

**CONCLUSION**

To a certain extent, moxibustion is likely to manage the symptoms and improve the QOL among the selected patients with KOA. Additionally, more well-designed, rigorous, randomized controlled trials on this subject are required to confirm the outcome validity of this meta-analysis.

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**REFERENCES**

1. Dawson J, Linsell L, Zondervan K, et al. Impact of persistent hip or knee pain on overall health status in elderly people: a longitudinal population study. *Arthritis Rheum.* 2005;53:368–374.
2. Xiang YJ, Dai SM. Prevalence of rheumatic diseases and disability in China. *Rheumatol Int.* 2009;29:481–490.
3. Felson DT, Lawrence RC, Deyo RA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med.* 2000;133:635–646.
4. Nelson FR. A background for the management of osteoarthritic knee pain. *Pain Manag.* 2014;4:427–436.
5. Towheed TE, Maxwell L, Iudd MG, et al. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev.* 2006:CD004257.
6. Deng H, Shen X. The mechanism of moxibustion: ancient theory and modern research. *Evid Based Complement Alternat Med.* 2013;2013:379291.
7. Yang MX, Zhao L, Yang J, et al. Bibliometrics analysis on researches of illness spectrum for acu-moxibustion therapy and prospect. *Zhong Ci Yan Jiu.* 2014;39:247–251.
8. Choi TY, Kim TH, Kang JW, et al. Moxibustion for rheumatic conditions: a systematic review and meta-analysis. *Clin Rheumatol.* 2011;30:937–945.
9. Zhang R. History and current state of moxibustion. *Zhong Xi Yi Jie He Xue Bao.* 2004;2:466–473.
10. Yuan QL, Guo TM, Liu L, et al. Traditional Chinese medicine for neck pain and low back pain: a systematic review and meta-analysis. *PLoS One.* 2015;10:e0117146.
11. Su JC, Cao LH, Li ZD, et al. Controlled clinical trials of initial observation on therapeutic effects of moxibustion for osteoarthritis of the knee: multi-center clinical effect. *Zhongguo Gu Shang.* 2009;22:914–916.
12. Wu F, Zhang R, Shen X, et al. Preliminary study on pain reduction of monosodium iodoacetate-induced knee osteoarthritis in rats by carbon dioxide laser moxibustion. Evid Based Complement Alternat Med. 2014;2014:754304.

13. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011; Available from: www.cochrane-handbook.org (Accessed: June 1, 2015).

14. Collins NJ, Misra D, Felson DT, et al. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Outcome Survey and Arthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S208–S228.

15. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in osteoarthritis: a systematic review and meta-analysis. Rheumatology (Oxford). 2011;63(Suppl 11):S208–S228.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.

17. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. J Bone Joint Surg Am. 2005;97:1628–1634.

19. Balsheh H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–406.

20. Zhao L, Cheng K, Wang L, et al. Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: a randomized, double-blinded, placebo-controlled clinical trial. Arthritis Res Ther. 2014;16:R133.

21. Ren X, Yao C, Wu F, et al. Effectiveness of moxibustion treatment in quality of life in patients with knee osteoarthritis: a randomized, double-blinded, placebo-controlled trial. Evid Based Complement Alternat Med. 2015;2015:569523.

22. Chen R, Chen M, Su T, et al. Heat-sensitive moxibustion in patients with osteoarthritis of the knee: a three-armed multicentre randomised active control trial. Acupunct Med. 2015;33:262–269.

23. Kim TH, Kim KH, Kang JW, et al. Moxibustion treatment for knee osteoarthritis: a multi-centre, non-blinded, randomised controlled trial on the effectiveness and safety of the moxibustion treatment versus usual care in knee osteoarthritis patients. PLoS One. 2014;9:e101973.

24. Raisch DW, Troutman WG, Sather MR, et al. Variability in the assessment of adverse events in a multicenter clinical trial. Clin Ther. 2001;23:2011–2020.

25. Pach D, Brinkhaus B, Willich SN. Moxa sticks: thermal properties and possible implications for clinical trials. Complement Ther Med. 2009;17:234–246.

26. Yu D, Xie HW, Zhang B, et al. Observation on clinical effects of moxibustion stimulation of different sensitive status acupoints for knee osteoarthritis. Zhen Ci Yan Jiu. 2013;38:497–501.

27. Lee MS, Choi TY, Kang JW, et al. Moxibustion for treating pain: a systematic review. Am J Chin Med. 2010;38:829–838.

28. Choi TY, Choi J, Kim KH, et al. Moxibustion for the treatment of osteoarthritis: a systematic review and meta-analysis. Rheumatol Int. 2012;32:2969–2978.

29. Hempel S, Suttrop MJ, Miles JNV, et al. Empirical Evidence of Associations Between Trial Quality and Effect Size [Internet]. Rockville, MD: Agency for Healthcare Research and Quality; 2011 :Report No.: 11-EHC045-EF.

30. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106:337–345.

31. de CWAC, Davies HT, Chadury Y. Simple pain rating scales hide complex idiosyncratic meanings. Pain. 2000;85:457–463.

32. Rossini M, Viapiana O, Ramonda R, et al. Intra-articular clodronate for the treatment of knee osteoarthritis: dose ranging study vs hyaluronic acid. Rheumatology (Oxford). 2009;48:773–778.

33. Perrot S, Bertin P. Feeling better” or “feeling well” in usual care of hip and knee osteoarthritis pain: determination of cutoff points for patient acceptable symptom state (PASS) and minimal clinically important improvement (MCII) at rest and on movement in a national multicenter cohort study of 2414 patients with painful osteoarthritis. Pain. 2013;154:248–256.

34. Kingsbury SR, Conaghan PG. Current osteoarthritis treatment, prescribing influences and barriers to implementation in primary care. Prim Health Care Res Dev. 2012;13:373–381.

35. Xie XJ, Jiao L, Fu Y, et al. Clinical effect of different schemes of mild moxibustion for treatment of knee osteoarthritis. Zhen Ci Yan Jiu. 2014;39:496–499.

36. Lin LM, Wang SF, Lee RP, et al. Changes in skin surface temperature at an acupuncture point with moxibustion. Acupunct Med. 2013;31:195–201.

37. Xu PC, Lee TL, Cui SL. Impacts on the skin temperature by the different distances of moxibustion: discussion on the safe distance of moxibustion. Zhongguo Zhen Jiu. 2012;32:611–614.

38. Ren XM, Cao JJ, Shen XY, et al. Knee osteoarthritis treated with moxibustion: a randomized controlled trial. Zhongguo Zhen Jiu. 2011;31:1057–1061.

39. Zhang CY, Shao FR, Cui RL, et al. Effects of Moxibustion on Expression of STAT 1, SOCS mRNA in Synovium of Rats with Rheumatoid Arthritis. Zhen Ci Yan Jiu. 2015;40:205–209.

40. Peng Y, Yi SX, Feng YS, et al. Serumimmunological study of moxibustion on helicobacter pylori gastritis in rats. Zhongguo Zhen Jiu. 2014;34:783–790.

41. Chu JH. How does moxibustion possibly work? Evid Based Complement Alternat Med. 2013;2013:198584.

42. Kim JH, Kim HK, Park YI, et al. Moxibustion at ST36 alleviates pain in complete Freund’s adjuvant-induced arthritic rats. Am J Chin Med. 2006;34:57–67.

43. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med. 2012;172:1444–1453.

44. Selfe TK, Taylor AG. Acupuncture and osteoarthritis of the knee: a review of randomized, controlled trials. Fam Community Health. 2008;31:247–254.

45. Berman BM, Lao L, Langenberg P, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med. 2004;141:901–910.

46. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different distances of moxibustion: discussion on the safe distance of moxibustion. Acupunct Med. 2015;40:205–209.

47. Uchida S, Suzuki A, Kagitani F, et al. Effect of moxibustion on hyaluronic acid. Rheumatology (Oxford). 2013;154:248–256.

48. Rossini M, Viapiana O, Ramonda R, et al. Intra-articular clodronate for the treatment of knee osteoarthritis: dose ranging study vs hyaluronic acid. Rheumatology (Oxford). 2009;48:773–778.

49. Gao L, Chen M, Yue P, et al. Effect of warm-needle moxibustion on hyaluronic acid. Zhong J Tradit Chin Med. 2015;40:229–232.
50. Yuan J, Hu L, Song XG, et al. Influence of moxibustion on TLR 4-MyD 88-NF-κB signal transduction pathway of synovial tissue in rheumatoid arthritis rats. *Zhen Ci Yan Jiu*. 2015;40:199–204.

51. Lee S, Kim KH, Kim TH, et al. Moxibustion for treating knee osteoarthritis: study protocol of a multicentre randomised controlled trial. *BMC Complement Altern Med.* 2013;13:59.

52. Zhao B, Wang X, Lin Z, et al. A novel sham moxibustion device: a randomized, placebo-controlled trial. *Complement Ther Med.* 2006;14:53–60; discussion 61.

53. Zhao BX, Chen HY, Shen XY, et al. Can moxibustion, an ancient treatment modality, be evaluated in a double-blind randomized controlled trial? – a narrative review. *J Integr Med.* 2014;12:131–134.

54. Kim SY, Yi SH, Cho JH, et al. Heat stimulation on the skin for medical treatment: can it be controlled? *J Altern Complement Med.* 2011;17:497–504.

55. Egger M, Smith GD. Bias in location and selection of studies. *BMJ*. 1998;316:61–66.

56. Ernst E, Pittler MH. Alternative therapy bias. *Nature*. 1997;385:480.

57. Sood A, Knudsen K, Sood R, et al. Publication bias for CAM trials in the highest impact factor medicine journals is partly due to geographical bias. *J Clin Epidemiol.* 2007;60:1123–1126.