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

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ABSTRACT

The purpose of this study was to evaluate the evidence supporting the effectiveness of moxibustion treatment for osteoarthritis. There were 9 databases used to retrieve randomized controlled trials (RCTs) that used moxibustion as treatment for osteoarthritis. The quality of methodology for the RCTs was assessed using the Cochrane Risk of Bias tool [Review Manager (RevMan) Version 5.3 Windows, The Nordic Cochrane Centre, Copenhagen, Denmark]. The inclusion criteria for this review was met by 27 RCTs. All studies were conducted in China. A 4-week moxibustion treatment period was the most common. EX-LE4 and SP10 and GB34 acupoints were most frequently selected in the treatment of osteoarthritis. The most commonly used evaluation index was the visual analog scale (VAS). All studies, including a meta-analysis showed that moxibustion treatments were statistically significantly effective at treating knee osteoarthritis. However, well-designed randomized RCTs without a high risk of bias should be designed in the future.

Introduction

Osteoarthritis is a degenerative disease characterized by the erosion of joint cartilage, hardening of the subchondral bone, bone hypertrophy, and joint deformation due to changes in cartilage metabolism of the joint and increased physical pressure [1]. Osteoarthritis is most common in knee joints that are directly subject to weight load [2]. Osteoarthritis causes chronic pain, stiffness, joint instability, and limited range of motion [3]. The prevalence of osteoarthritis is higher in older age, and in Korea, about 80% of patients over 55 years old, and almost all elderly people (65 years and older) have knee osteoarthritis [4]. As an aging society, the prevalence of osteoarthritis is expected to increase.

Osteoarthritis treatment primarily focuses on conservative treatments such as exercise, weight loss, heat therapy, non-steroidal anti-inflammatory drugs, and intra-articular injections of hyaluronic acid [5]. Surgical treatment may be performed if there is severe pain, joint instability, and movement limitations due to severe degenerative changes [5]. In traditional Korean medicine (which is a representative conservative treatment), various treatments such as moxibustion, acupuncture, pharmacopuncture, and herbal medicine are used to treat osteoarthritis. In Korea, fire needling treatment of osteoarthritis, and Bee venom treatment of osteoarthritis have been reported [6,7]. However, there are no systematic reviews or meta-analyses of moxibustion treatment of
osteoarthritis in Korea.

Moxibustion is a representative Korean medicine treatment that promotes blood circulation by burning wormwood in acupuncture points, and is used in various musculoskeletal disorders including osteoarthritis [8].

The purpose of this study was to investigate the effects of moxibustion treatment of knee osteoarthritis through a systematic review and meta-analysis to understand the effectiveness of moxibustion treatment. Randomized controlled trials (RCTs) of moxibustion treatment for osteoarthritis were retrieved using national and international databases, and analyzed to review research trends and effectiveness of treatment.

Materials and Methods

Search strategy
PubMed, EMBASE, the Cochrane library, Citation Information by NII (CiNii), China National Knowledge Infrastructure (CNKI), Korean Medical database (KMBASE), Korean studies Information Service System (KISS), National Digital Science Library (NDSL), the Korean database Oriental medicine Advanced Searching Integrated System (OASIS) were searched to retrieve related articles until the 10th August, 2019.

The subject search terms were based on “Medium Subject Headings (MeSH)” including “arthritis,” “osteoarthritis,” “knee joint,” “degenerative arthritis,” “knee,” “moxibustion,” “moxa,” and “randomized controlled trial.” The actual search term was modified according to the language of each database.

Eligibility criteria

Inclusion criteria
The purpose of this study was to determine whether moxibustion treatment was an effective treatment for knee osteoarthritis. This study included RCTs applying moxibustion treatment to osteoarthritis. There were no restrictions on the language or the year of publication of the papers. In order to confirm the effect of the thermal stimulation of moxibustion treatment, no limitation was placed on the type of moxibustion, and the method of treatment. Although comparative interventions included treatments other than moxibustion, studies that analyzed the effectiveness of moxibustion treatments were included in this study.

Exclusion criteria
Literature reviews, case reports, observational research, animal experiment research, management studies after surgery (e.g. knee replacement), studies on treatment methods that are not commonly practiced in Korean medicine, studies conducted in children and adolescents were excluded. Moxibustion studies in both the intervention group and the control group, or studies comparing moxibustion types were excluded because the effectiveness of moxibustion treatments could not be compared. In addition, studies in which only abstracts were available, but not the original article were excluded.

Data collection and risk of bias
Studies that met the selection criteria and 2 reviewers independently assessed and extracted the data. If there was any discrepancy, it was re-evaluated by a third party with similar qualifications as the 2 reviewers. To assess the bias risk of the RCTs, the Cochrane risk of bias tool (RoB) was used.

Statistical analysis
To summarize the effects of moxibustion treatments for knee osteoarthritis in each study, the Cochrane Collaboration software [Review Manager (RevMan) Version 5.3 for Windows, The Nordic Cochrane Centre, Copenhagen, Denmark] was used. The relative risk, the standardized mean difference, the mean difference and the 95% confidence interval were calculated. The results of the included studies were synthesized using a fixed effect model.

Results

Study selection
As a result of the database search, a total of 869 articles were retrieved (PUBMED 114, EMBASE 150, Cochrane 169, CiNii 84, CNKI 217, KMBASE 16, KISS 16, NDSL 44, OASIS 15, and 44 additional records identified through other sources). Of these, 260 duplicated articles were removed, and the primary screening was conducted on 609 articles to exclude studies that were not related to knee osteoarthritis, non-clinical studies, and non-RCTs which was performed by reading the titles and abstracts leaving 511 studies. As a result of checking full texts, 98 articles remained, from which a total of 69 articles were excluded, including 17 articles that did not contain the original text, 1 article that did not meet the selection criteria for the intervention and control group, and 51 articles that set improper groups. Finally, a total of 27 articles were selected from this systematic literature review, and meta-analysis were conducted. The selection process is illustrated using the flow chart of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Fig. 1).

Year of publication

Sample size of study
There was a total of 2,175 patients included in the RCTs in the 27 articles included in this review. In each study, the total number of patients in both intervention and control groups was at least 31 and at most 185. There was 1 study with less than 50, 19 studies with more than 50 and less than 100, 6 studies with more than 100 and less than 150, and 1 study with more than 150.

Duration and frequency of treatment
Ten studies had a treatment duration of less than 4 weeks and 16 studies had more than 4 weeks. There was 1 study with 10 weeks of treatment [9]. One study did not report the exact duration of treatment [10].

The sessions of treatment were to some extent proportional to the duration of treatment. There were 2 studies with less than 10 sessions of treatment, 12 studies with more than 10 and less than 20 sessions of treatment, and 11 studies with more than 20 sessions of treatment. There were 2 studies that did not report the exact number of treatments [10,11].

Frequency of acupuncture
As a result of analyzing selected acupoints in the intervention group, EX-LE4 was the most frequently selected (16 times in the
Evaluation index

The most commonly used evaluation index was the visual analog scale (VAS) which was used as an evaluation scale in 12 studies. Effective rate was used as an evaluation index for 11 studies. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used as an evaluation index in 8 studies, and Short Form 36 (SF-36) was used in 2 studies. In addition to these evaluation indexes, numerical rating scale (NRS), and knee-joint function scores (IAC Lennox, Lysholm) were used. The results are summarized in Table 1 [9-35].

Analysis of treatment effect

In most studies, the intervention group showed better results after treatment than in the control group. However, Zhang et al [14] showed good treatment effects using VAS and total effective rate, but there was no mention of $p$ value, which made it difficult to determine statistical significance. In the study of Zhou et al [23], the effective rate immediately after treatment and 2 months after treatment was significantly higher in the intervention group than in the control group ($p < 0.05$). However, the pain scores measured by VAS did not differ significantly between the 2 groups. In the study of Cheng et al [10] using the NRS as an evaluation index, both the intervention group and the control group showed significant pain reduction, but there was no statistically significant difference. In the study of Wu and Xiong [25], there was no difference in the effective rates of the interventional group (heat-sensitive acupoint moxibustion) and control group (intra-articular injection), but heat-sensitive acupoint moxibustion showed a faster treatment effect. In all other studies except for the study by Zhou et al [15] and Wu et al [16], which did not mention the $p$ value, the intervention group showed a statistically significant improvement over the control group.

Analysis of side effect

As a result of analyzing adverse events in the intervention group, adverse events were not reported in 19 studies. In 1 study, adverse events were reported (skin flushing), but the patients’ symptoms disappeared within 3 days, and without any treatment [27]. The remaining 7 studies reported adverse events but none were recorded.

Risk of bias

For the 27 RCTs included in this review, 2 researchers evaluated the risk of bias by applying the Cochrane risk assessment tool [risk of bias (RoB) by Cochrane collaboration] to each study. Evaluation of all items was accepted only when the contents of the selected study were clearly stated. In case of disagreement between evaluators, there was sufficient discussion and other researchers’ opinions were reflected upon. The results of the bias risk assessment are plotted using the Revman program (Figs. 2 and 3).

Random sequence generation

There were 18 Low-Risk studies in which random assignments were made using random number tables and lottery tickets. The remaining 8 studies were classified as Unclear Risk because only the expression “random assignment” existed, and there was no mention of the process of random assignment. Only 1 study [21] had a High Risk of bias. This was because odd numbers were assigned to the intervention group and even numbers were assigned to the control group and odd and even numbers were assigned in the order of the visit.

Allocation concealment

In 5 studies [16,24,27,29,32], the risk of bias was Low Risk. The opaque sealed envelope was assigned a serial number and the assignment order was kept. The remaining studies did not mention the allocation order concealment, so they were classified as an Unclear Risk.

Blinding of participants and personnel

Of the 27 studies, 22 were classified as High Risk. This was because of the nature of moxibustion treatment was difficult to
<table>
<thead>
<tr>
<th>First author (y) [ref]</th>
<th>Sample size, total (T.C)</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Outcome measurement</th>
<th>Summary of results</th>
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</thead>
<tbody>
<tr>
<td>Wang (2015) [9]</td>
<td>60 (30:30)</td>
<td>Ginger moxibustion (n = 30)</td>
<td>Glucosamine sulfate potassium capsule 0.75 g/d + intra-articular injection (sodium hyaluronate, 2 mL/week) (n = 30)</td>
<td>WOMAC (total)</td>
<td>(I vs C, baseline-immediate post treatment) WOMAC total: 69.3 ± 5.25±13.7 vs 17.27 (p &lt; 0.01) vs 69.3 ± 5.58+45.67 ± 13.22 (p = 0.01), IG vs CG (p = 0.012)</td>
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<td>Cheng (2008) [10]</td>
<td>120 (60:60)</td>
<td>Moxibustion (n = 60)</td>
<td>Diclofenac sodium 75 mg/d (n = 60)</td>
<td>NRS</td>
<td>(I vs C, baseline-immediate post treatment) NRS: 6.42 ± 2.32 vs 1.13 ± 0.87 (p &lt; 0.01) vs 6.31 ± 2.41±1.28 ± 0.85 (p &lt; 0.05), IG vs CG (ns)</td>
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<td>Zhang (2015) [11]</td>
<td>185 (48:46:43:48)</td>
<td>IG: Moxibustion (n = 48)</td>
<td>CG1: Rehabilitation therapy (n = 46)</td>
<td>NRS</td>
<td>(I vs C1 vs C2 vs C3, Baseline→ immediate post treatment) WOMAC: 32.47 ± 3.91 ± 8.85 vs 44.2 ± 7.24 vs 29.36 ± 5.28, IG vs C1 vs C2 (p &lt; 0.05), IG vs C3 (NS)</td>
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<td>Ren (2011) [12]</td>
<td>59 (31:28)</td>
<td>Moxibustion (n = 31)</td>
<td>Placebo moxibustion (n = 28)</td>
<td>WOMAC score</td>
<td>(I vs C, Baseline→12 wk after treatment) WOMAC: 32.42 ± 16.97±12.67 ± 7.51 (p &lt; 0.01) vs 26.94 ± 13.13±22.47 ± 15.41, IG vs CG (p &lt; 0.01)</td>
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<tr>
<td>Zhao (2013) [13]</td>
<td>87 (35:33:19)</td>
<td>IG1: moxibustion (n = 35)</td>
<td>Celebrex 0.2 g/d (n = 19)</td>
<td>VAS</td>
<td>(I vs C1 vs C2, C3, C4, Baseline→ immediate post treatment) WOMAC: 3.41 ± 1.73 vs 3.43 ± 1.89 ± 1.47, IG1 vs CI vs C2 vs C3, C4 (p &lt; 0.05)</td>
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<tr>
<td>Zhang (2011) [14]</td>
<td>60 (30:30)</td>
<td>Moxibustion (n = 30)</td>
<td>Celecoxib 200 mg/d (n = 30)</td>
<td>VAS</td>
<td>(I vs C, immediate post treatment) VAS: 2.76 ± 1.95 ± 3.07 ± 1.62 ± 3.65 ± 1.42</td>
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<tr>
<td>Zhou (2014) [15]</td>
<td>105 (39:44:22)</td>
<td>Moxibustion (n = 39)</td>
<td>CG1: EA (n = 44) CG2: Celecoxib 0.2 g/d (n = 22)</td>
<td>VAS</td>
<td>(I vs C1 vs C2, immediate post treatment) VAS: 5.1 ± 1.33 ± 5.1 ± 1.63 ± 25 (83.6%) vs 26 (30, 86.6%)</td>
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<tr>
<td>Wu (2011) [16]</td>
<td>31 (15:16)</td>
<td>Laser moxibustion</td>
<td>Sham laser moxibustion</td>
<td>SF-36</td>
<td>(I vs C, Baseline→8 wk after treatment) SF-36: 60.67 ± 6.78±75 ± 13.09 (p &lt; 0.05) vs 60.67 ± 15.65+65.31 ± 13.96</td>
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<tr>
<td>Sun (2008) [17]</td>
<td>56 (29:27)</td>
<td>Aconitum cake-separate moxibustion (n = 29)</td>
<td>Sodium dichloroacetate slow-released tablet 75 mg/d (n = 27)</td>
<td>Effective rate</td>
<td>(I vs C, immediate post treatment, 10 wk after treatment) 1) effective rate: 39.4/1 vs 35.3/9, IG vs CG (NS) 2) markedly effective rate: 26/41 (63.4%) vs 19/39(48.7%), IG vs CG (p &lt; 0.05)</td>
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<tr>
<td>Deng (2015) [18]</td>
<td>70 (35:35)</td>
<td>Salt moxibustion (n = 35)</td>
<td>Ibuprofen 0.6 g/d (n = 35)</td>
<td>WOMAC (total)</td>
<td>(I vs C, immediate post treatment) WOMAC total: 22.63 ± 9.54 ± 31.22 ± 8.62, IG vs CG (p &lt; 0.05)</td>
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<tr>
<td>Yuan (2015) [19]</td>
<td>148 (74:74)</td>
<td>Heat-sensitive point Thunder-fire moxibustion (n = 74)</td>
<td>Medication (diclofenac sodium enteric-coated tablet, 100 mg/d)</td>
<td>VAS</td>
<td>(I vs C, immediate post treatment) VAS: 24.07 ± 2.83 ± 36.22 ± 2.32, IG vs CG (p &lt; 0.01)</td>
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<tr>
<td>First author</td>
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<td>Deng (2015) 20</td>
<td>80 (40:40)</td>
<td>Salt moxibustion</td>
<td>Ibuprofen 0.6 g/d</td>
<td>VAS</td>
<td>(I vs C, baseline-immediate post treatment) VAS: 6.89 ± 1.28±0.98 ± 0.63 (p &lt; 0.05) vs 7.08 ± 2.06→ 1.01 ± 0.86 (p &lt; 0.05), IG vs CG (p &lt; 0.05)</td>
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<td>Yang (2008)  21</td>
<td>64 (33:31)</td>
<td>Notoginseng cake-separated moxibustion</td>
<td>Diclofenac sodium sustained release tablets 75 mg/d</td>
<td>Effective rate (IG vs CG (p &lt; 0.05))</td>
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<tr>
<td>Song (2013)  22</td>
<td>80 (40:40)</td>
<td>Notoginseng cake-separated moxibustion</td>
<td>Diclofenac sodium sustained release tablets 75 mg/d</td>
<td>WOMAC (pain, stiffness, function)</td>
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<tr>
<td>Zhou (2010)  23</td>
<td>70 (35:35)</td>
<td>Notoginseng cake-separated moxibustion</td>
<td>Diclofenac sodium sustained release tablets 75 mg/d</td>
<td>Effective rate 1) IG vs CG (p &lt; 0.05)</td>
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<tr>
<td>Ren (2015)   24</td>
<td>136 (69:67)</td>
<td>Moxibustion</td>
<td>Sham moxibustion</td>
<td>SF-36</td>
<td>(I vs C, Baseline→12 wk after treatment) 1) SF-36 PF (physical): 57.83 ± 16.88→63.99 ± 18.24 (p &lt; 0.01) vs 60.15 ± 17.21→66.04 ± 14.42 (p &lt; 0.01) 2) SF-36 RP (physical): 33.7 ± 37.33→57.49 ± 43.48 vs 42.91 ± 41.7→45.15 ± 40.88 3) SF-36 RE (mental): 49.76 ± 44.14→57.49 ± 43.87 vs 56.22 ± 41.52→50.25 ± 44.71 4) SF-36 VT (physical &amp; mental): 53.35 ± 18.19 (p &lt; 0.01)→ 59.42 ± 15.87 vs 52.99 ± 18.55→54.91 ± 3.09 5) SF-36 MH (mental): 78.62 ± 18.7→79.17 ± 13.33 vs 68.78 ± 15.84→66.99 ± 14.43 6) SF-36 SF (physical &amp; mental): 58.55 ± 12.82→67.54 ± 14.45 vs 75.16→78.54 ± 15.05 7) SF-36 BP (physical): 6.73 ± 2.35→3.03 ± 2.33 (p &lt; 0.001) vs 57.69 ± 18.49→65.93 ± 13.53 (p &lt; 0.01) 8) SF-36 GH (physical &amp; mental): 50.29 ± 15.31→54.42 ± 15.92 (p &lt; 0.05) vs 47.99 ± 15.88→46.43 ± 12.01</td>
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<td>Wu (2011)     25</td>
<td>50 (24:26)</td>
<td>Heat-sensitive acupoint moxibustion</td>
<td>Intra-articular injection (sodium hyaluronate 2 mL/week)</td>
<td>Effective rate (I vs C, baseline→immediate post treatment)</td>
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<tr>
<td>Chi (2016)    26</td>
<td>120 (40:40:40)</td>
<td>Heat-senitization acupoint moxibustion</td>
<td>CG1: Moxibustion</td>
<td>CG2: intra-articular sodium hyaluronate injection 2 mL/6 d</td>
<td>Effect rate (I vs C)</td>
</tr>
<tr>
<td>Zhao (2014)   27</td>
<td>110 (55:55)</td>
<td>Moxibustion</td>
<td>Sham moxibustion</td>
<td>WOMAC score</td>
<td>(I vs C, Baseline→24 wk after treatment)</td>
</tr>
<tr>
<td>Bu (2018)     28</td>
<td>62 (31:31)</td>
<td>Heat-sensitive acupoint moxibustion</td>
<td>Diclofenac sodium gel</td>
<td>VAS</td>
<td>(I vs C, baseline→immediate post treatment) VAS: 8.34 ± 0.98±2.01 ± 0.28 (p &lt; 0.05) vs 8.12 ± 1.05→ 5.76 ± 0.71 (p &lt; 0.05), IG vs CG (p &lt; 0.05)</td>
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Table 1. (Continued).

<table>
<thead>
<tr>
<th>First author</th>
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</tr>
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<tbody>
<tr>
<td>Zhou (2017) [29]</td>
<td>60 (30:30)</td>
<td>Moxibustion + placebo gel 12 g/d (n = 30)</td>
<td>Placebo moxibustion + diclofenac sodium gel 12 g/d (n = 30)</td>
<td>1) WOMAC 2) VAS</td>
<td>(I vs C, baseline+4 wk after treatment) 1) WOMAC total: 35.47 ± 15.45 vs 35.73 ± 7.68 p &lt; 0.05 vs 35.73 ± 7.68 vs 24.57 p &lt; 0.05 IG vs CG (p = 0.043) 2) WOMAC pain: 8.07 ± 3.36 vs 4.07 ± 2.16 (p &lt; 0.05) vs 8.41 ± 2.29 vs 4.37 ± 1.4 (p &lt; 0.05) IG vs CG (p = 0.32) 3) WOMAC stiffness: 2.03 ± 1.99 vs 1.07 ± 1.23 (p &lt; 0.05) vs 2.07 ± 1.26 vs 1.5 ± 0.84 (p &lt; 0.05) IG vs CG (p &lt; 0.05) 4) WOMAC function: 24.37 ± 11.43 vs 25.27 ± 5.13 ± 18 vs 3.93 (p &lt; 0.05) IG vs CG (p = 0.036) 5) VAS: 3.98 ± 1.2 vs 3.81 ± 1.18 ± 1.89 ± 2.42 ± 0.86 (p &lt; 0.05) vs 4.45 ± 1.01 ± 2.67 ± 0.61 (p &lt; 0.05) IG vs CG (p = 0.183)</td>
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<td>Zhang (2009) [30]</td>
<td>60 (30:30)</td>
<td>Moxibustion (n = 30)</td>
<td>Placebo moxibustion + diclofenac sodium gel 12 g/d (n = 30)</td>
<td>Effective rate</td>
<td>(I vs C, immediate post treatment) Effective rate: 83.33% vs 80%. IG vs CG (p &lt; 0.01)</td>
</tr>
<tr>
<td>Zheng (2017) [31]</td>
<td>60 (30:30)</td>
<td>Acupuncture + ginger moxibustion (n = 30)</td>
<td>Acupuncture (n = 30)</td>
<td>VAS</td>
<td>(I vs C, baseline+immediate post treatment) VAS: 7.37 ± 1.56 vs 7.1 ± 1.69 p &lt; 0.05 vs 3.13 ± 1.53 (p &lt; 0.05) IG vs CG (p &lt; 0.05)</td>
</tr>
<tr>
<td>Zhang (2010) [32]</td>
<td>62 (32:30)</td>
<td>Non-scarring moxibustion + acupuncture (n = 32)</td>
<td>Acupuncture (n = 30)</td>
<td>1) Effective rate 2) VAS</td>
<td>(I vs C, immediate post treatment) 1) Effective rate: 30/32 (93.8%) vs 26/30 (86.7%). IG vs CG (p &lt; 0.05) 2) VAS: 0.63 ± 0.35 vs 1.23 ± 1.18. IG vs CG (p &lt; 0.01)</td>
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<tr>
<td>He (2009) [33]</td>
<td>60 (30:30)</td>
<td>Moxibustion + diclofenac sodium 75 mg/d (n = 30)</td>
<td>Diclofenac sodium 25 mg/d (n = 30)</td>
<td>Effective rate</td>
<td>(I vs C, immediate post treatment) Effective rate: 27/30 (90%) vs 20/30 (66.67%). IG vs CG (p &lt; 0.01)</td>
</tr>
<tr>
<td>Tian (2017) [34]</td>
<td>60 (30:30)</td>
<td>External application of indirect moxibustion + glucosamine 0.942 g/d (n = 30)</td>
<td>Glucosamine 0.942 g/d (n = 30)</td>
<td>Effective rate</td>
<td>(I vs C, immediate post treatment) Effective rate: 56.67% vs 33.33%. IG vs CG (p &lt; 0.05)</td>
</tr>
<tr>
<td>Xiao (2017) [35]</td>
<td>60 (30:30)</td>
<td>Moxibustion + intra-articular injection (sodium hyaluronate 2 mL/wk) (n = 30)</td>
<td>Intra-articular injection (sodium hyaluronate 2 mL/wk) (n = 30)</td>
<td>VAS</td>
<td>(I vs C, 1 month after treatment) VAS: 3.81 ± 1.18 vs 3.98 ± 1.92. IG vs CG (p &lt; 0.05)</td>
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</table>

C, Control; CG, control group; EA, electroacupuncture; I, intervention; IG, intervention group; NRS, numeric rating scale; NS, not significant; RCT, randomized controlled trial; SF-36, medical outcomes study 36-item short form health survey; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

blind. There were 5 studies [12,16,24,27,29] which had a Low Risk of bias due to double blinding.

**Blinding of outcome assessment**
There were 3 studies [24,27,29] that had a Low Risk of bias because the study was blinded to the reviewer, but the other studies had an Unclear Risk of bias because there were no remarks on the related contents.

**Incomplete outcome data**
All 27 studies were classified as Low Risk because they had no missing values because the total number of participants in the intervention group and the control group matched before and after the study.

**Selective reporting**
All 27 studies had a protocol for the study and the risk of bias was Low Risk because the study handled the results in a predetermined way.

**Other bias**
Since there was no risk of additional bias, all 27 studies were classified as Low Risk.

**Meta-analysis result**
Moxibustion versus sham moxibustion
Meta-analysis of all 27 studies comparing moxibustion with sham moxibustion showed statistically significant results when using the
Fig. 2. Risk of bias summary for randomized controlled trials.

Fig. 3. Risk of bias for randomized controlled trials.

Fig. 4. The meta-analysis of moxibustion versus sham moxibustion (WOMAC pain, stiffness, function).

WOMAC, Western Ontario and McMaster Universities Arthritis Index.
Fig. 5. The metaanalysis of moxibustion versus conventional Western medicine (VAS, WOMAC total).
VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
Fig. 6. The meta-analysis of moxibustion versus conventional Western medicine (WOMAC pain, stiffness, function).
WOMAC, Western Ontario and McMaster Universities Arthritis Index.
WOMAC evaluation index (p < 0.0001), WOMAC index for stiffness (p = 0.02), and WOMAC index for function (p = 0.007; Fig. 4).

Moxibustion versus conventional Western medicine

The meta-analysis of studies comparing moxibustion with conventional Western medicine (analgesic, glucosamine, injection, ointment) showed that moxibustion treatment was statistically significantly more effective when using the VAS score for pain (p < 0.00001), the WOMAC index total (p = 0.25), WOMAC index for pain (p < 0.0001), WOMAC index for stiffness (p < 0.0001), WOMAC index for function (p = 0.002), and the effective rate of the moxibustion treatment (p < 0.00001) compared with conventional Western medicine (Figs. 5-7).

Moxibustion with conventional Western medicine versus conventional Western medicine alone

The meta-analysis of studies of moxibustion treatment with conventional Western medicine comparing with studies of conventional Western medicine alone, showed that the intervention group had no statistically significant effect compared with the control group in pain reduction (VAS; p = 0.68), but moxibustion treatment was statistically significantly more effective when the effective rate (p = 0.001) was used compared with conventional Western medicine (Fig. 8).

Moxibustion with conventional Korean medicine versus conventional Korean medicine without moxibustion

The meta-analysis of studies of moxibustion treatment with conventional Korean medicine compared with studies of conventional Korean medicine without moxibustion.
conventional Korean medicine without moxibustion showed that both pain reduction (VAS; $p = 0.0004$) and the effective rate of treatment ($p = 0.04$) showed statistically significant improvement when moxibustion was used for treatment (Fig. 9).

**Discussion**

The purpose of this study was to evaluate the effect of moxibustion treatment for osteoarthritis of the knee. There were 27 RCT studies selected for this review based on a preselected selection and exclusion criteria, using 9 online databases. All 27 selected studies were conducted in China. According to the purpose of the study, there were 21 studies comparing moxibustion with Western medicine. There were 4 studies comparing moxibustion with a placebo control, and 2 studies comparing moxibustion with Korean medicine. Celecoxib,
diclofenac, ibuprofen, glucosamine, and sodium hyaluronate were used as the Western medicine group. Among them, diclofenac was used in 10 studies.

All the treatments used in the Korean medicine group were acupuncture. EX-LE4, ST35, GB34, and ST35 were the most selected acupoints. In addition, most of the acupoints around the knee were commonly used.

VAS, effective rate, WOMAC, SF-36, NRS, and Knee Function Score were used as the evaluation index, and VAS (the measure of pain) was used the most. Typically, the intervention group in most studies showed improvement over the control group after treatment. Zhang et al. [14] showed good treatment effects using both the VAS and the total effective rate: 5.1 ± 1.33 in the intervention group, 5 ± 1.63 in the control group, and 83.3% in the intervention group, 86.6% in the control group. However, it was difficult to judge statistical significance because there was no mention of p-value. In the study of Zhou et al. [23], the markedly effective rates immediately after treatment and 2 months after treatment showed a statistically significant difference of 58% in the intervention group, and 27.1% in the control group (p < 0.05). However, the pain score measured by the VAS was 5.53 ± 1.46 in the intervention group, and 5.31 ± 1.55 in the control group. There was no significant difference between the 2 groups. In the study by Cheng et al. [10] using the NRS as an evaluation index, the score changed from 6.42 ± 2.32 to 1.13 ± 0.87 in the intervention group, and 6.31 ± 2.41 to 1.28 ± 0.85 in the control group which...
showed significant pain reduction after treatment compared with before treatment. However, there was no statistically significant difference. The total effective rate of the study by Wu and Xiong [25] was 95.8% in the intervention group (heat-sensitive acupoint moxibustion) and 100% in the control group (intra-articular injection). There was no significant difference between the 2 groups, but heat-sensitive acupoint moxibustion had a faster treatment effect.

One of the 27 studies showed side effects (skin flushing) in the moxibustion treatment group. The remaining 19 studies did not mention measurement of adverse events or side effects. The remaining 7 studies reported no adverse reactions after moxibustion. However, moxibustion treatment is a therapy that applies heat stimulation, so there was a risk of burns which always requires the attention of the clinician.

Analyzes from the Cochran bias risk assessment tool “RoB” by Cochrane collaboration determined that the majority of the studies used a random number table or a lottery table to assign the order of placement. Thus, the risk of bias was Low Risk in most studies. Most studies, however, did not mention allocation concealment and blinding of outcome assessment. In addition, due to the nature of moxibustion as interventional treatment tool, there was a limit to blinding of participants and personnel.

According to the study design, RCTs could be classified into 4 types: RCTs comparing moxibustion with sham moxibustion, RCTs comparing moxibustion with conventional Western medicine, RCTs comparing the intervention group that combined moxibustion and conventional Western medicine with the control group that performed only conventional Western medicine, and RCTs comparing the intervention group that combined moxibustion with conventional Korean medicine with the control group that performed conventional Korean medicine without moxibustion.

As a result of meta-analysis, moxibustion treatment compared with sham moxibustion showed statistically significant results in the WOMAC index (pain, stiffness, function). In addition, moxibustion treatment compared with conventional Western medicine showed statistically significant results in the VAS, WOMAC index (pain, stiffness, function), and effective rate. The combination of moxibustion treatment and Western medicine showed a significant effect in the effective rate measure compared with the control group using only Western medicine, but did not have a significant effect in the pain reduction scale (VAS score). RCTs combined with moxibustion treatment and conventional Korean medicine showed statistically significant effects on both the effective rate and the VAS score compared with the control group that performed conventional Korean medicine without moxibustion.

This study confirmed that moxibustion treatment had a statistically significant effect on knee osteoarthritis. However, researches from other databases and unpublished research are not included in this review. All the selected studies for this review were conducted in China which may limit the validity of moxibustion efficacy through objective meta-analysis. In addition, because there were many studies using subjective evaluation indicators and lack of common evaluation indicators, there were limitations in comparing and interpreting the results. In the future, standardized evaluation indicators are needed. In the results related to the risk of bias, there were items which were not mentioned, and there was a limit in the capacity to blind the study participants. So, in order to confirm the effectiveness of moxibustion treatment further research is needed into research design to minimize the risk of bias.

In conclusion, based on the results of this systematic review and meta-analysis, moxibustion can be considered as a treatment for knee osteoarthritis.

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

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**References**


