Moxibustion for Chronic Pelvic Inflammatory Disease：A systematic review and meta-analysis

Abstract

Background: This study was performed to strictly evaluate the quality of RCTs and thus test the effect of moxibustion on CPID. **Methods:** Seven databases (PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, WangFang Database, Chinese Scientific Journal Database, Chinese Biomedical Literatures Database were reviewed for RCTs on CPID treated by moxibustion up to September 2020. Methodological quality and evidence level was assessed on the basis of the RoB tool from Cochrane collaboration and the GRADE instrument, respectively. RevMan5.4.1 and Stata 12.0 software were used for further meta-analysis.

Results: A total of 17 RCTs were included (1315 participants, 515 treated by moxibustion and 515 treated by control therapy). The meta-analysis showed that, in comparison to control group, moxibustion had a higher total effective rate (RR = 1.21; 95% CI [1.31, 1.29]; P = 0.007; I^2 = 53%); and lower total symptom score (MD = -3.72; 95% CI [-4.38, -3.06]; P =0.02; I^2 = 66%). As for the total sign score, the participants treated by moxibustion had lower scores than those treated by control therapy(SMD = -0.72; 95% CI [-1.07, -0.37]; P = 0.36; I^2 = 0%). For the VAS score, pelvic fluid and inflammatory factor level, only one trial showed that there was a significant effect, respectively. The adverse events in the moxibustion group were mainly burns and blisters, which healed quickly after timely treatment.

Conclusions: This study shows that moxibustion is more effective and safe for CPID. The findings we obtained must be interpreted with caution due to universal low quality and low evidence level of the eligible trials.

Trial registration number: CRD42020158744 in PROSPERO 2020.

Keywords: chronic pelvic inflammatory disease, moxibustion, systematic review, meta-analysis, systematic review

Tweetable abstract: Through systematic review and meta-analysis, moxibustion was more effective and safe for treating CPID.

1. Introduction

Chronic pelvic inflammatory disease (CPID)[1] is a clinical issue of women reproductive system featured by pelvic pain, menstrual disorder along with various symptom in the lower urinary tract, which worsening after fatigue or sexual intercourse. Women with CPID are more likely to have poor health, depression, low energy levels, ovarian tumours and sexual problems than those without the condition[2].

Worldwide, the incidence rate of PID is close to 2% ~ 12%, which has a rising trend.[3,4] In NHANES 2013–2014 in the U.S.A, the prevalence of lifetime PID reported by women themselves was 4.4%, indicating that about 2.5 million women between 18–44 years old have been diagnosed with PID in their lifetime[5]. Studies have shown that the incidence of secondary infertility is as high as 10% ~ 20%, which represents CPID become a source of serious reproductive problems for women in childbearing age[6,7]. The cost of CPID treatment is huge, it is reported that the average annual medical expenditure per case had grown to as much as $3,025 in America [8] and £163 in HongKong[9].

CPID can be caused by microbial infections, muscle or bone disease in the pelvic area, and neuropsychiatric problems, which pathogenesis are still tricky to illustrate.[10] There is an explanation that it would occur when microorganisms, such as chlamydia trachomatis and neisseria gonorrhoeae, move from the vagina or cervix to the fallopian tubes or other structures of the upper reproductive tract[11].

Western medicine recommends antibiotics or non-steroidal anti-inflammatory drug, and surgical treatment if necessary. Finite evidence supports the use of western medicine for chronic pelvic pain, such as antibiotics and nonsteroidal anti-inflammatory drugs, while evidence-based therapy remains limited[12]. What's more, patients who take these drugs over a long period in large doses may experience side effects and tolerance to the drugs[13]. As for surgery, the iatrogenic uterine injury may occur after the operation[14]. Due to the inadequacy of treatments above, many

CPID patients turn to safe and effective alternatives.

According to the TCM theory, it is mainly caused by the damp invasion of lower energizer and qi stagnation and blood stasis[15]. Moxibustion, a long-used TCM treatment, is widely explored on account of its safety and effectiveness. It includes many types, such as heat-sensitive moxibustion, warm-needling, spreading medicinal moxibustion, thunder fire moxibustion, herb—partitioned moxibustion and so on. Many clinical trials using the kinds of moxibustion above have been conducted to treat CPID, for example, J.L.Jin[23] treated 30 cases of CPID with warm-needling moxibustion, and Y.J.Xie etc.[29]selected ginger moxibustion to observe the clinical effect of CPID. It is thought to stimulate the blood circulation utilizing warming, promotes the inflammation to subside, regulate the body function state bidirectionally and enhance the body's immune function[16]. X.G.Nong etc.[17] proved that moxibustion combined with ligustrazine could significantly reduce the levels of CRP, IL-6 and TNF-α in patients with CPID. Z.Q.Su[31] compared the mild moxibustion group with the control group, then found that the levels of serum IgG, IgA and IgM of the patients showed an increasing trend, indicating that moxibustion had a significant regulatory effect on serum immunoglobulin of patients with CPID.

Nowadays, the application of moxibustion therapy for CPID is limited on account of efficacy controversy. No SRs or Meta-analysis of moxibustion therapy for CPID has been published currently. Hence, we attempted to evaluate the effect of moxibustion compared with other treatments by meta-analysis in order to achieve a wider application and provide clinicians with some direction to manage CPID in moxibustion.

2. Methods

2.1. Protocol and Registration.

This review was pre-registered in the PROSPERO, the protocol of which can be searched from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020158744, and carried out rigorously according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[18].

2.2. Eligibility Criteria

2.2.1. Types of Studies.

RCTs of moxibustion for CPID were selected. The following categories of literature were not included in the selection: 1)duplicate publication; 2)case series; 3)non-controlled trials; 4)animal studies; 5)review articles; 6)conference papers.

2.2.2. Patients.

Participants over 18 years of age, given the diagnosis of CPID defined by authoritative diagnostic criteria or references. No limitation on syndrome type, duration, and severity.

2.2.3. Types of Interventions.

Heat-sensitive moxibustion, spreading medicinal moxibustion, warm-needling, thunder fire moxibustion, herb—partitioned moxibustion, moxibustion combined with western medicine or conventional therapy, and any other type of moxibustion were eligible in our study. Excluded therapies were the RCTs of moxibustion used as an ancillary treatment.

2.2.4. Types of Comparisons.

Control measures should be positive therapy (e.g., western medicine, conventional therapy or Chinese patent medicine used maturely in the clinic), no treatment or placebo. Excluded therapies were the RCTs as follows: acupuncture, Chinese herb or different types of moxibustion.

2.2.5. Types of Outcome Measures.

The primary outcome was the total effective rate. Secondary outcomes of interest consisted of (1) total symptom score; (2) total sign score; (3) VAS (visual analog scale); (4) pelvic fluid; (5) inflammatory factor level; and(6) adverse events.

According to *the guidelines for Clinical Research of New Traditional Chinese Medicine*[19], total symptom score includes 8 quantitative projects: (1) lower abdomen pain belly, (2) the lumbosacral pain, (3) abnormal down, (4) abdominal pain is aggravated by overwork and sexual intercourse as well as before and after menstruation(5) god fatigue, (6) defecate pond drainage, (7) tongue, and (8) pulse condition, a total of 57 points. Total sign score consists of 5 items as follows:

(1)uterine body activity restriction or tenderness, (2)tubal tenderness, (3)pelvic connective tissue inflammatory change, (4)accessory mass and tenderness, and (5)inflammatory changes of the ligaments of the uterine skeleton, a total of 12 points. The comprehensive score of signs and symptoms is 69.

The severity of CPID was assessed in strict accordance with the standards above. For mild cases, the total score was ≤23; for moderate cases, the total score was 24-46; for severe cases, the total score was > 46.

2.3. Study identification and selection.

PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang, VIP, and CBM were searched from the date of the establishment of to September 2, 2020 without any language restriction. The main keywords contain "moxibustion," "chronic pelvic inflammatory disease," and "RCT." Besides, the relevant journals and bibliographies were searched manually. The comprehensive search strategy took PubMed as an example and presented in Table 1.

2.4. Selection Process.

Literature obtained through retrieval were saved into NoteExpress. Republished studies were first ruled out. Then, two reviewers (Fanghui Hua, Shouqiang Huang) independently selected the relevant research by title and abstract. And finally included the researches by reading the full text. In case of disagreement between them, the third researcher shall arbitrate (Xiang).

2.5. Data Extraction and Management.

A pre-designed table for data extraction were made up and based on the PICOS principle. Two researchers (Huang and Xiang) extract data from the selected trials. and cross-check repeatedly. If there was any disagreement, arbitration would be made by a third person(Xiong). The information we need included the following sides: general information, average age, sample size, intervention, control, outcome, and adverse events. When necessary information was not available, we would use the ways we can to contact the author for acquiring information.

2.6. Assessment of Methodological Quality.

Two reviewers(Zhou and Hua) assessed the risk based on included RCTs on the basis

of Cochrane Reviewer's Handbook[20], which consists of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluator, incomplete outcome data, selective outcome reporting, and other biases. Each of them was scored as high (H), low (L), and unclear (U). The disagreement was settled by discussion or decision by the other author(Xiong).

2.7. Data Synthesis and Analysis.

We used RevMan 5.4.1 software to analyze the data. Continuous variables were analyzed using mean difference(MD) with 95% CI; categorical variables were analyzed using the relative ratio (RR) with 95% CI. Statistical heterogeneity was assessed by Chi-square test and I^2 value. A fixed-effect model was selected when $P > 0.1$ and $I^2 < 50\%$; otherwise, when $I^2 > 50\%$, subgroup analysis was adopted to resolve methodological and clinical heterogeneity. When there was heterogeneity that could not be readily explained, a random effect model was considered. We performed a sensitivity analysis of all indices to test the stability of the results when necessary. When the number of eligible RCTs exceeds 10, the Egger test is used to determine potential publication bias[21].

2.8. Level of Evidence.

The total effective rate, total symptom score and the total sign score improvement were also evaluated using levels of evidence as determined by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[22]. The level of evidence was lowered gradually from high, moderate, low, to very low on the basis of five domains: risk of bias, inconsistency, directness, imprecision, and publication bias.

3. Results

3.1. Search Results.

1420 articles were initially screened, and finally, 17 RCTs meeting the criteria were included. NoteExpress 3.0 software was used to sort out and filter the studies, and the literature that were not satisfied with the inclusion criteria were removed. Figure 1 shows a PRISMA flow of the selection process.

3.2. Study Characteristics.

Table 2 presented the characteristics information we selected.

3.2.1. Types of Studies.

All the studies were published in Chinese, none in English or in other languages. Three trials[25,31,38] were masters theses, and rest trials were published in peer-reviewed journals.

3.2.2. Types of Intervention.

6 trials [24-29] used warming needle treatment, 2 RCT [33,34] adopted Thunder fire moxibustion, 4 RCT [35-36] adopted herb-partitioned moxibustion, 1 RCT[39] used moxibustion, 1 RCT[32] selected heat-sensitive moxibustion, 1 RCT[30] compared Ginger partition moxibustion to western medicine, 1 RCT[23] used spreading medicinal moxibustion and 1 RCTs [31] used Mild moxibustion.

3.2.3. Types of Control.

7 RCTs [23-25,31,32,36,39] used Chinese patent medicine western medicine treatment, 9 RCTs[26-30,33-35,37] compared with western medicine treatment, and 1 RCTs[38] compared with flour—partitioned moxibustion.

3.2.4. Types of Outcome Measures.

16 RCTs [23-37,39] published the total effective rate, 5 RCTs [23,25,29-31] selected total symptom score, 2 RCTs [25,38] selected total sign score, 1 RCT [30] measured pain intensity by VAS, 1 RCT [34] assessed pelvic fluid, 1 RCT [30] reported inflammatory factor level and 5 RCT [23,25,27,29,36] reported adverse events.

3.3. Risk of Bias Assessment.

(1) Randomization: 8 RCTs[23,30,31,34,36-39] adopted random number table, 1 RCT [35] was randomized by random allocation of data function of Excel and 8 RCTs [24-29,32,33] simply mentioned random words; (2) allocation hiding: none of 17 RCTs had an explanation about allocation hiding; (3) blind method: Only 1 trial[38] was performed in a single-blind; (4) selective report: all RCTs reported predetermined outcome measures; and (5) follow-up and abscission: all cases were fully reported in all RCTs. The risk of bias assessment is presented in Table 3 and Figures 2 and 3.

3.4. Outcomes

3.4.1. Total Effective Rate.

Meta-analysis of 16 [23-37,39] out of 17 RCTs involving 1285 participants showed that it had a significant difference between the moxibustion and the control group in curative effect (RR = 1.21; 95% CI [1.31, 1.29]; P = 0.007; I^2 = 53%) with higher heterogeneity, as presented in Figure 4.

3.4.2. Total Symptom Score.

Meta-analysis of 5 [23,25,29-31] out of 17 RCTs involving 311 participants showed that it had a significant difference between the moxibustion and the control group in symptom improvement (MD = -3.72; 95% CI [-4.38, -3.06]; P =0.02; I^2 = 66%) with higher heterogeneity (Figure 6).

3.4.3. Total Sign Score.

The total sign score was illustrated in 2 [25,38] RCTs with 136 participants. Meta-analysis prove that it had a significant difference between the moxibustion and the control group in sign improvement (SMD = -0.72; 95% CI [-1.07, -0.37]; P = 0.36; I^2 = 0%) (Figure 6).

3.4.4. VAS Score.

One study[30] reported VAS after 12 weeks of treatment. Ginger partition moxibustion provided a better improvement in pain compared with conventional therapy ($P < 0.05$).

3.4.5. Inflammatory factor level.

One RCT [30] reported that after 12 weeks of treatment, there was a significant difference in CRP, TNF-α and IL-2 between ginger partition moxibustion and conventional therapy ($P < 0.05$).

3.4.6. Pelvic Fluid

Only 1 RCT [36] was included. And the results showed a significant improvement in reducing pelvic effusion between two groups ($P < 0.05$) after two periods of treatment.

3.4.7. Adverse Events.

Five studies[25,26,27,29,36] reported adverse events. There were no obvious adverse reactions or accidents reported in two RCTs[25,27]. One[36] reported that 1 patient in moxibustion treatment developed skin blistering coated with iodophor and recovered

after 1 week. One[29] reported that in the experiment group, there was 1 case of muscle soreness and 1 case of dizziness, and the incidence of adverse reactions was 6.67%. In the control group, there was only 1 case of nausea and vomiting, and the incidence of adverse reactions was 3.33%. There was no significant difference between the two groups (2 = 0.3509, P > 0. 05). In the remaining RCT[26], dizziness and headache occurred in 4 patients, nausea and vomiting in 2 patients, muscle soreness in 2 patients. After adjusting drug dosage and time of treatment, the adverse reactions disappeared. Besides, both groups had mild adverse reaction symptoms, which did not affect the therapeutic effect.

3.4.8. Publication Bias.

Due to the problem of sample size, we only evaluated the total effective rate of publication bias. The analysis, which was made through Egger's test from STATA 12.0 software, showed that the total efficacy of moxibustion had a particular publication bias (P = 0.000 < 0.05, and the 95% CI [1.57, 4.19] did not contain 0). (Figures 7)

3.4.9. Subgroup Analyses.

Due to the limited number of studies included, we were unable to conduct subgroup analysis.

3.4.10. Sensitivity Analysis.

Sensitivity analysis was performed using STATA 12.0 software to determine the stability of the meta-analysis. For the effective rate, after the exclusion of Zhang's study in 2014[26], the comparison results of heterogeneity were significantly reduced(RR = 1.17, 95% CI = 1.12, 1.23, P = 0.25, I^2 =18%), as presented in Figures 8. As for the total symptom score, the comparison results of heterogeneity were significantly reduced (MD = -3.94, 95% CI = -4.42, -3.47, P = 0.20, I^2 =36%) by omitting the study by Su made in 2009[31], as presented in Figures 9. Therefore, we regard these two studies as the source of heterogeneity of the effective rate and total symptom score, respectively.

3.5. Level of Evidence.

Using the GRADE, we found the evidence quality was low or very low, which

reduced the intensity of our recommendations for results. The levels were reduced mainly from three aspects: the risk of bias, inconsistency, and imprecision (Table 4).

4. Discussion

4.1. Summary of evidence.

In this review, the total effective rate, total symptom score and total sign score of moxibustion were better than that of the control groups, which included western medicine, conventional drugs and placebo. The outcome indicators set before, which consisted of the VAS score, pelvic fluid, and inflammatory factor levels, selected in this study were only descriptive analysis because only one RCT was included. The results above also showed that moxibustion was better than the control group.

4.2. Quality of Evidence.

The risk bias assessment from Cochrane indicated that the quality of the included RCTs was generally low. There were 3 cases of medium quality and 14 cases of low quality. Incorrect random method, allocation concealment and unimplemented blind method exaggerate the results of the result measurement. Because moxibustion could not perform blind operation well, we suggested that at least as far as possible, the outcome assessment and statistics should be conducted single-blind. Due to the low level of evidence from the GRADE table, we recommended moxibustion to treat CPID finitely.

4.4. Discussion of Heterogeneity.

Meta-analyses showed substantial heterogeneity among the pooled trials about the total effective rate and total symptom score. Because subgroup analysis could not be performed, we adopted the sensitivity analysis method to explore its source and found that the heterogeneity was significantly reduced after omitting the study of Zhang[26], and Su[31]. We attempted to reduce heterogeneity by conducting sensitivity analyses, as well as analyzing the characteristics of interventions and controls, finally found several problems from the study of Zhang[26], and Su[31] as below: 1) low quality; 2) small sample size; 3) defects in the test design; 4)different evaluation criteria and standard.

4.2. Limitations and Strengths.

Our study had some limitations as follows:

(1) Due to the limited quantity of included RCTs and imperfection of outcome indicators, the subgroup analysis was not carried out according to the possible variables set before, and the evidence intensity may be affected. For many indicators, such as “inflammatory factor level”, only one studies can be included, which may give rise to an unreliable inference of the results. So, it's hard to draw conclusion from the results of this study.

(2) Given that search conditions were limited and moxibustion belongs to the category of TCM, the research in this field has not been seen abroad. And Egger’s test indicated that there was a certain degree of publication bias.

(3) Although we conducted a comprehensive search in seven different databases with no language restrictions and eventually collected a large amount of literature, we cannot guarantee that all relevant RCTs will be included in the review.

(4) The methodological quality and the level of evidence included in the studies was generally poor, according to the result of the RoB tool and GRADE evidence profiles. The majority of the included RCTs had an unclear risk of bias in random sequence generation, allocation concealment and blinding of participants/practitioners/outcome assessors. Though it is undeniable that moxibustion may have potential efficacy in treating CPID, more high-quality RCTs are needed to prove it.

The study also has some significant advantages, as described below:

First of all, as SRs and Meta-analysis about moxibustion for CPID had not been done before this study, this is the first one developed in this area. Secondly, we carried out this review in rigorous accordance with PRISMA guidelines to make the content conform to the standard. Thus, we expected that this review could provide evidence to make it convincing that moxibustion can effectively and safely treat CPID, which would benefit clinical treatment.

5. Conclusion

Based on this review’s evidence, we found that moxibustion has some advantages on the treatment of CPID compared to western medicine or conventional therapy. To further validate this result and provide reliable evidence of the efficacy of

moxibustion for CPID, future RCTs should have large samples, multiple centers and adhere to rigorous standards, such as CONSORT[40] and STRICTOM guidelines[41].

Abbreviations: CPID = chronic pelvic inflammatory disease, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, CI=confidence interval, SR=systematic review, VAS=visual analog scale

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Acknowledgments

We are very grateful to the study participants who took the time to participate.

Authors' Contributions

Fanghui Hua, Shouqiang Huang, Jie Xiang and Xiaohong Zhou extracted the data. Fanghui Hua prepared the original draft. Jun Xiong reviewed and edited the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Ethical approval

Not required.

Funding

This work was supported by the National Natural Science Foundation of China (82060893, 81573835) and "One Thousand Talents Plan" for Introducing and Training High-level Innovative and Entrepreneurial Talents in Jiangxi Province -- the first batch of Training High-level Scientific and Technological Innovative Talents (Youth) Project (jxsq2019201104).

Figure Legends

Table 1: PubMed: searched on September 2, 2020.

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Table 1: PubMed: searched on September 2, 2020.

Number	Search terms
#1	MeSH: “Moxibustion”
#2	Ti/Ab: “Moxibustion”
#3	#1 OR #2
#4	MeSH: “ pelvic inflammatory disease ”
#5	Ti/Ab: “ chronic pelvic inflammatory disease” OR “chronic pelvic inflammation” OR “chronic pelvic infection” OR “chronic endometritis” OR “sequelae of pelvic inflammatory disease” OR “pelvic inflammatory disease” OR “chronic salpingitis” OR “chronic parametritis”
#6	#4 OR #5
#7	MeSH: “randomized controlled trial” OR “randomized controlled trial as Topic” OR “controlled clinical trial”
#8	Ti/Ab: “randomized controlled trial” OR “controlled clinical trial” OR “randomized”
#9	#7 OR #8
#10	#3 AND #6 AND #9

Table 2: Basic characteristics of eligible RCTs.

Study ID	**Age**	**Intervention**		**Sample Size**	**Period**	**Adverse events**	**outcome**
		Treatment	**Control**	**T/C**			
Zhang 2020[23]	T:36.95± 7.18 C:35.25± 8.74	spreading medicinal moxibustion+Guizhi Fuling Capsules	Guizhi Fuling pills	40/40	8 weeks	Unclear	Total effective Rate, Total symptom score
Jin 2009[24]	T:20-45 C:19-43	warming needle	Baoguang Fule granules	30/30	2 menstrual cycles	Unclear	Total effective rate
Lu 2018[25]	T:35.28±4.72 C:34.97±4.95	warming needle	fuke Qianjin tablets	53/53	3 months	Non	Total effective rate, Total symptom score, Total sign score
Zhang 2014[26]	T/C: 35±2.5 (20-50)	warming needle	penicillin	40/40	30 days	①	Total effective rate
Qin 2016[27]	T:35.7± 2.7 C:34.5± 2.9	warming needle	levofloxacin	50/50	14 days	Unclear	Total effective rate
Wu 2014[28]	T:21 - 48 C:20 - 49	warming needle	cefuroxime sodium	30/30	20 days	Unclear	Total effective rate

Zhou 2016[29]	T:32 ± 2. 52 C:33±2. 41	warming needle	penicillin	30/30	30 days	②	Total effective rate, Total symptom score
Xie 2018[30]	T:29.2±5.8 C:29.6±5.2	Ginger partition moxibustion	levofloxacin hyd rochloride	33/32	12 weeks	Unclear	Total effective rate, Total symptom score, VAS score, Inflammatory factor level
Su 2009[31]	/	Mild moxibustion	fuke Qianjin tablets	30/30	2 months	Unclear	Total effective rate, Total symptom score, VAS score
Wang 2008[32]	/	Heat-sensitive moxibustion	fuke Qianjin capsule	30/30	30 days	Unclear	Non
Gu 2009[33]	T:21-47 C:22-45	Thunder fire moxibustion+doxycycline +azithromycin	doxycycline +azithromycin	41/42	30 days	Unclear	Total effective rate
Mai2015[34]	T:44.68± 10.59 C:43.82±10.31	doxycycline +Thunder fire moxibustion	doxycycline	62/62	7 weeks	Unclear	Total effective rate
An 2014[35]	T:26-49 C:26-48	herb—partitioned moxibustion	levofloxacin +metronidazole	30/30	30 days	Unclear	Total effective rate
Chen 2013[36]	T:35±8 C:34±8	herb—partitioned moxibustion	fuke Qianjin tablets	40/40	2 months	③	Total effective rate, pelvic fluid
Zhang 2015[37]	T:35.9±7.35 C:35.1±7.99	herb—partitioned moxibustion	tinidazole+azithromycin	62/60	30 days	Unclear	Total effective rate
Yang 2015[38]	T:32.53±6.15 C:31.73±5.81	herb—partitioned moxibustion	flour—partitioned moxibustion	15/15	2 months	Unclear	Total sign score
Zhao 2019[39]	T:35.06±3.25 C:34.59±3.81	moxibustion	kangfu xiaoyan suppository	40/40	28 days	Unclear	Total effective rate

①dizziness, headache, nausea, vomiting and muscle soreness; ②muscle soreness, dizziness, nausea and vomiting; ③skin blistering

Table 3: Risk of bias in the included RCTs.

Study ID	Random sequence generation	Allocation concealment	Blinding		Outcome data integrity	Low risk	Other biases
			Patient/doctor blinding	Outcome assessor blinding			
Zhang 2020[23]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Jin 2009[24]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Lu 2018[25]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Zhang 2014[26]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Qin 2016[27]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Wu 2014[28]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Zhou 2016[29]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Xie 2018[30]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Su 2009[31]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Wang 2008[32]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Gu 2009[33]	Random word	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Mai2015[34]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
An 2014[35]	Excel	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Chen 2013[36]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Zhang 2015[37]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain
Yang 2015[38]	Random number	Uncertain	Low risk	Uncertain	Low risk	Low risk	Uncertain

	table						
Zhao 2019[39]	Random number table	Uncertain	Uncertain	Uncertain	Low risk	Low risk	Uncertain

Table 4: Level of evidence.

Variable (study number)	Sample size (T/C)	I^2 value (%)	*P* value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect (95% CI)	Level of evidence
Total effective rate	644/641	53	0.007	Serious①	Non	Non	Serious③	Serious④	RR=1.21; 95%CI [1.31, 1.29]	Low⊕⊕○○
Total symptom score	156/155	66	0.02	Serious①	Serious②	Non	Serious③	Non	MD= -3.72; 95% CI [-4.38, -3.06]	Low⊕⊕○○
Total sign score	68/68	0	0.36	Serious①	Serious②	Non	Serious③	Non	MD= -0.72; 95% CI [-1.07, -0.37]	Low⊕⊕○○

①None of the following is mentioned: Blind method, allocation hidden report, and random method description; ②statistical heterogeneity and clinical heterogeneity were more significant; ③the total sample size was small, and OIS(optimal information size) was not satisfied; ④Egger' s test($P < 0.05$, and the 95% CI [1.57, 4.19] did not contain 0) means the possibility of publication bias was stronger. ⊕⊕○○ represents the level is low. ⊕○○○ represents the level of very low.