Systematic Review and Meta-Analysis

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The efficacy and safety of simple-needling for the treatment of primary dysmenorrhea compared with ibuprofen

A systematic review and meta-analysis

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Abstract

Background: Needling and ibuprofen are often used clinically to treat primary dysmenorrhea (PD). However, the difference between the efficacy and safety of the treatment of PD is not clear. This study evaluates the efficacy and safety of simple-needling for PD patients through a comparison with ibuprofen.

Methods: A comprehensive search of 7 electronic databases and relevant medical journals, from the establishment of the publication to December 2020. The Cochrane risk of bias tool was used to evaluate the methodological quality of randomized clinical trials (RCTs) that met the inclusion criteria, and a meta-analysis was performed with the Review Manager version (RevMan version 5.3).

Results: Twenty three RCTs were included. The meta-analysis reported that simple-needling groups had better than ibuprofen groups on cure rate (relative risk = 2.29, 95% CI [1.96, 2.68], $P < .00001$) and total effective rate (relative risk = 1.24, 95% CI [1.19, 1.29], $P < .00001$) and VAS score (MD = −1.24, 95% CI [−1.92, −0.55], $P = .0004$). Seven studies reported adverse events, of which 4 studies had mild adverse events.

Conclusion: Simple-needling is superior to ibuprofen treatment in terms of clinical efficacy and improvement of pain symptoms. A small number of studies reported whether simple-needling produced adverse events, so there is not enough evidence to support the safety of simple-needling in the treatment of PD.

PROSPERO registration number: CRD42021233403

Abbreviations: ITT = intention to treat, NSAIDs = nonsteroidal anti-inflammatory drugs, PD = primary dysmenorrhea, PG = prostaglandin, RCTs = randomized clinical trials, RR = relative risk, VAS = visual analogue scale.

Keywords: ibuprofen, meta-analysis, primary dysmenorrhea, randomized clinical trials, simple-needling

1. Introduction

Dysmenorrhea is a common gynecological disease, it can be divided into primary dysmenorrhea (PD) and secondary dysmenorrhea. PD is no obvious organic disease of the reproductive system.[1] The main clinical manifestations are lower abdominal pain, swelling, and backache before and after or during menstruation.[2] In severe cases, it may be accompanied by fatigue, dizziness, nausea[3] and has an unignorable impact on women's personal quality of life, work and study efficiency.[4–8] Moreover, long-term pain experience may lead to maladaptive brain structure plasticity, which in turn affects psychological adjustment, making patients more vivid when witnessing the pain and suffering of others.[9] The disease is very common in women, and the incidence of people of different ages and ethnicities is

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between 45% and 97%.[10] Recent epidemiological studies have reported that the prevalence of PD among female college students in China is 51.1%.[11] The prevalence of dysmenorrhea is 51.5% for female college students in Ethiopia.[12] The pathogenesis of PD involves many unexplained mechanisms and the exact cause of the disease is not fully understood. However, it has been recognized that PD is due to uterine spasmodic contractions and focal ischemia, and uterine ultrasound has not shown any visible lesions. The increased synthesis of prostaglandin (PG) leads to rhythmic uterine contractions and decreased blood flow is one of the currently accepted explanations. During menstruation, PG will contract the endometrial vessels and the smooth muscle of the myometrium, and excessive release of PG will cause ischemia-reperfusion and lead to dysmenorrhea.[13] Non-steroidal anti-inflammatory drugs (NSAIDs) seem to be an effective way to treat PD, reducing pain by inhibiting the production and release of PG.[14] However, long-term use of NSAIDs can produce adverse reactions to a certain extent, such as drowsiness, dizziness, headache, vomiting, acute asthma, gastrointestinal bleeding, acne, etc.[15] Among various treatment methods, complementary and alternative therapies for PD have attracted worldwide attention.[16,17] In the field of complementary medicine, acupuncture, Chinese herbal medicine, yoga, Tuina, and hypnosis have been used to treat PD.[18–21] Acupuncture has been introduced as an effective non-drug therapy.[22] Acupuncture treatment can inhibit the synthesis and secretion of PG in the venous blood of patients with dysmenorrhea, and then relieve or weaken the abnormal contraction of uterine smooth muscle, thereby achieving the purpose of eliminating or reducing pain.[23] In recent years, acupuncture treatment has attracted the attention of researchers studying PD. Several studies have evaluated the effectiveness and safety of acupuncture in the treatment of PD.[24–28] However, it is worth noting that in the reviews, the use of acupuncture combined with various interventions may conceal or exaggerate the therapeutic effect of acupuncture. Ibuprofen as a representative NSAID for the treatment of PD. Therefore, the purpose of this systematic review and meta-analysis is to examine the clinical evidence of the therapeutic effect of simple-needling on PD in clinical trials and compare it with ibuprofen.

2. Methods

2.1. Study registration

This systematic review and meta-analysis were registered in PROSPERO (CRD42021233403) at https://www.crd.york.ac.uk/Prospero/.

2.2. Inclusion criteria

2.2.1. Types of studies. Randomized clinical trials (RCTs) that had tested simple-needling for PD were be included. There were no restrictions for blinding and follow-up. Publications in English and Chinese were included.

2.2.2. Types of participants. Participants diagnosed with PD were not restricted by age, region, or race, but must have clear diagnostic criteria and efficacy criteria. The treatment course was limited to 3 menstrual cycles.

2.2.3. Types of interventions. Experimental interventions were simple-needling. It involved piercing a needle into the skin to stimulate a specific part of the body to achieve the therapeutic goal. The treatment time and frequency of needling were not limited. The intervention measures of the control groups were ibuprofen, the specification and dosage of ibuprofen were not restricted.

2.2.4. Types of outcome measures. The studies reported that any of the following 4 outcome indicators could be included. Cure rate, markedly effective rate, total effective rate (the curative effect was divided into cured, markedly effective, effective, ineffective, total effective as effective and all cases above effective), visual analog scale (VAS) score (referring to the internationally recognized visual analog pain scale).

2.3. Search strategy

We searched 4 Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, Wanfang database, Chinese Science and Technology Periodical Database) and 3 English databases (PubMed, the Cochrane Library, Embase). All English and Chinese studies from the establishment of the journal to December 2020. At the same time, further searches were conducted on medical journals related to non-electronic. The detailed search strategy for PubMed is shown in Table 1. Identical search strategies will be used for other electronic databases.

2.4. Data collection and analysis

2.4.1. Selection of studies. We imported all retrieved documents into Endnote X9, and deleted duplicate studies. Two researchers independently screened the studies. First, they checked the titles, abstracts and keywords of the studies and deleted the studies that did not meet the inclusion criteria. Second, they obtained the full-text content of the remaining studies and deleted the studies that were beyond the inclusion criteria by reading the full text. The selection results were cross-checked by 2 researchers. Any differences should be reached through discussion with the third researcher.

2.4.2. Data extraction. First, 2 independent researchers extracted the following information based on the data extraction template formulated in advance: first author, publication year, country, intervention measures, dose, frequency, sample size, random method, allocation concealment, blinding, follow-up, clinical outcomes, adverse events. Next, the 2 researchers independently cross-checked the extracted information. If there was a difference, the third researcher would discuss and resolve it through consultation. If necessary, contact the original author for missing data.

Table 1

PubMed search strategy.

Number	Search terms
1	Needling
2	Acupuncture
3	Needle
4	1 or 2 or 3
5	Primary dysmenorrhea
6	Dysmenorrhea
7	Abdominal pain during menstruation
8	Premenstrual abdominal pain
9	5 or 6 or 7 or 8
10	Randomized controlled trial
11	Randomized controlled
12	Randomly
13	10 or 11 or 12
14	4 and 9 and 13

2.4.3. Assessment of risk of bias. Two researchers independently assessed the risk of bias in the included studies according to the latest version of the Cochrane Handbook.[29] It included the following aspects, namely random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting. A bias value of "high," "unclear," or "low" was given for each item. The 2 researchers need to cross-check the evaluation results, and any differences need to be discussed and resolved with the third researcher.

2.4.4. Data analysis. We used Review Manager (RevMan version 5.3) to analyze the extracted data. Measurement data was represented by Mean Difference, and count data was represented by Relative Risk (RR). The heterogeneity among the studies was analyzed by the Q test and I^2 test. $P \geq .10$, $I^2 < 50\%$, it was considered that there was no heterogeneity between the studies or the heterogeneity was small, and the fixed effect model was used for meta-analysis. $P < .10$, $I^2 \geq 50\%$, it was considered that there was a large heterogeneity between the studies, and the random effect model was used for meta-analysis. If the heterogeneity was obvious, sensitivity analysis would be used.

2.5. Sensitivity analysis

Sensitivity analysis will be conducted by sequential omitting a single study at a time to determine the factors that contribute the most to heterogeneity.

2.6. Publication of bias risk assessment

If the number of studies for pooling was more than 10, publication bias would be assessed using a funnel plot.

2.7. Ethics and dissemination

No ethical approval is required because this systematic review will be performed based on published studies.

3. Results

3.1. Studies screening process

A total of 2702 references were initially searched.66 references were selected after reading the title and abstract, and 23 studies were included in the overview after viewing full texts. The study selection process was shown in Figure 1. The characteristics of the included studies were shown in Table 2.

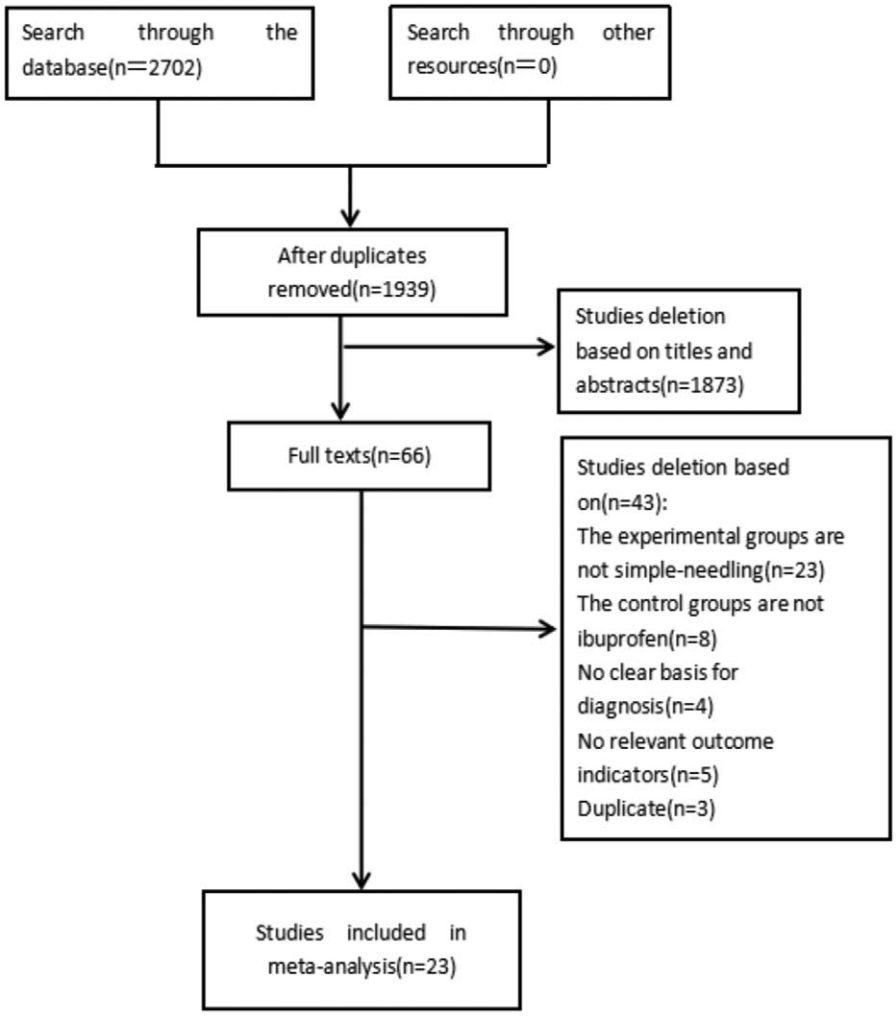

Figure 1. Studies screening flowchart.

Table 2

Characteristics of included studies.

Included studies	Years	Country	Sample size		Age	Intervention		Dose		Course of treatment	Outcome indicators	Follow up	Shedding
			Experimental group	Control group		Experimental group	Control group	Experimental group	Control group				
Hu et al[25]	2012	China	60	50	15–30	Eye acupuncture	Ibuprofen	1 time/d	300 mg/time,2 times/d	3 menstrual cycles	Cure rate; Total effective rate	3 menstrual cycles after treatment	No shedding
Zhi et al[26]	2007	China	57/57	57	Not reported	Electro-superficial-needling; superficial needling	Ibuprofen	1 time/cycle	0.3mg/time, 2 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	3 menstrual cycles after treatment	Shedding
Ren et al[27]	2010	China	30	30	12–48	electroacupuncture	Ibuprofen	1 time/d	300 mg/time, 2 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	No shedding
Wang et al[28]	2018	China	20	20	14–35	Abdominal Acupuncture	Ibuprofen	1 time/d	300 mg/time,2 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	No shedding
Liang et al[29]	2018	China	32	32	14–35	Abdominal Acupuncture	Ibuprofen	1 time/d	300 mg/time,2 times/d	3 menstrual cycles	VAS score	3 menstrual cycles after treatment	Shedding
Zhu[30]	2015	China	33	33	16–28	Abdominal Acupuncture	Ibuprofen	1 time/2 d	0.2 g/time, 1 time/d	3 menstrual cycles	VAS score; Cure rate; Markedly effective rate; Total effective rate	1 month after treatment	Shedding
Li[31]	2016	China	30; 30	30	16–35	Tongyuan acupuncture; conventional acupuncture	Ibuprofen	1 time/d	300 mg/time,2 times/d	3 menstrual cycles	VAS score; Cure rate; Markedly effective rate; Total effective rate	3 menstrual cycles after treatment	Not reported
Liang et al[32]	2018	China	30	30	16–25	Qin's flying needling	Ibuprofen	1 time/d	2 times/d, 2 capsules/time	3 menstrual cycles	VAS score; Cure rate; Total effective rate	Not reported	Not reported
Wang et al[33]	2013	China	32; 31	32	18–25	Wrist ankle needle; Conventional needling	Ibuprofen	1 time/d	300 mg/time,1 time/d	3 menstrual cycles	VAS score; Cure rate; Markedly effective rate; Total effective rate	Not reported	Shedding
Liu et al[34]	2011	China	30	30	18–41	needling Diji	Ibuprofen	1 time/2 d	300 mg/time,3 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	Not reported
Wei et al[35]	2016	China	30	30	10–30	Conventional needling	Ibuprofen	Not described	1 piece/time,1 time/d; In severe cases, take 2 tablets orally after 12 h	3 menstrual cycles	VAS score; Cure rate; Total effective rate	Not reported	Not reported
Li et al[36]	2017	China	20	20	15–30	needling Dong's odd points	Ibuprofen	1 time/day	300 mg/time,2 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	Not reported
Ning et al[37]	2015	China	45	45	16–37	Conventional needling	Ibuprofen	1 time/day	0.3 g/time, 2 times/d	3 menstrual cycles	Cure rate; Total effective rate	Not reported	Not reported
Fu et al[38]	2010	China	50	50	13–35	Conventional needling	Ibuprofen	1 time/day	1 capsule/time, 2 times/d	3 menstrual cycles	Cure rate; Total effective rate	Not reported	Not reported
Chen et al[39]	2011	China	52	40	14–43	Conventional needling	Ibuprofen	1 time/day	1–2 tablets/time, 2–3 times/d	3 menstrual cycles	Cure rate; Total effective rate	Not reported	Not reported
Zhao et al[40]	2011	China	40	40	18–42	Conventional needling	Ibuprofen	1–2 times/day	0.3 g/time, 2 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	Not reported
Chen et al[41]	2014	China	40	40	Not reported	Conventional needling	Ibuprofen	Not described	0.3 g/time, 2 times/d	3 menstrual cycles	VAS score; Markedly effective rate; Total effective rate	3 menstrual cycles after treatment	Not reported
Wang et al[42]	2014	China	31	32	18-25	Conventional needling	Ibuprofen	1 time/day	300 mg/time,1 time/d	3 menstrual cycles	VAS Cure rate; Markedly effective rate; Total effective rate	Not reported	Shedding
Wang et al	2019	China	32	32	18–35	Long needle	Ibuprofen	1 time/day	300 mg/time, 2 times/d	3 menstrual cycles	VAS score	Not reported	Shedding
Zhu et al	2019	China	36	36	16–30	Conventional needling	Ibuprofen	1 time/day	0.3 g/time, 2 times/d	3 menstrual cycles	Total effective rate	Not reported	Not reported
Sheng	2019	China	36	36	16–35	Conventional needling	Ibuprofen	1 time/day	200 mg/time,3 times/d	3 menstrual cycles	VAS score; Cure rate; Markedly effective rate; Total effective rate	3 menstrual cycles after treatment	Shedding
Shi et al	2020	China	30	30	15–36	Zhuang needling	Ibuprofen	2 time/wk	0.3g/time, 3 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	3 menstrual cycles after treatment	Not reported
Xue	2020	China	60	60	18–34	Conventional needling	Ibuprofen	1 time/d	0.3 g/time,3 times/d	3 menstrual cycles	Cure rate; Markedly effective rate; Total effective rate	Not reported	Not reported

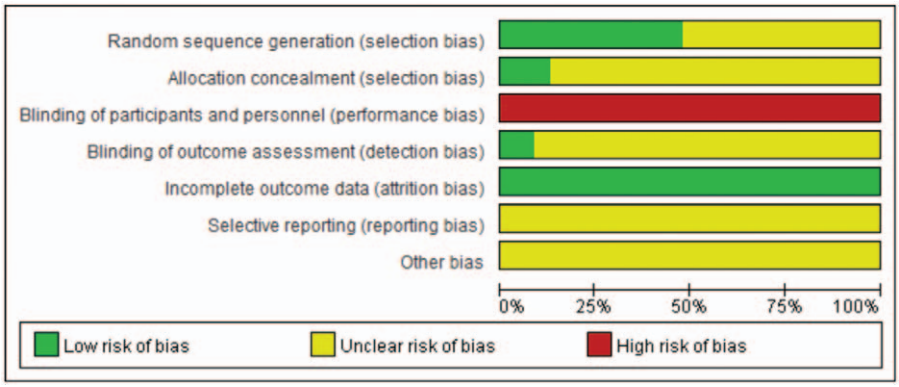

Figure 2. Risk of bias graph of included studies.

3.2. Risk of bias

The risk of bias for each included RCT was summarized in Figure 2 and Figure 3. For the random sequence generation, risk of bias for 11 RCTs[30,33,34,35,38,41,42,47,48,49,52] were rated as low and 12 RCTs[31,32,36,37,39,40,43,44,45,46,50,51] were rated as unclear. Only 3 RCTs[33,35,48] mentioned allocation concealment, while the remaining researches did not mention allocation concealment. Blinding of participants and personnel of bias were rated as high risk of bias in all included studies. Only 2 RCTs[34,48] reported blinding of outcome assessment. All of the RCTs had an unclear risk of bias in selective reporting and other sources of bias. In addition, only 7 studies[31,34,35,38,47,48,50] reported the numbers of withdrawals from the trials during the treatment course. Most of the included trials had no intention to treat (ITT) analysis, except for 2 RCTs.[31,48]

3.3. Meta-analysis outcomes

3.3.1. Clinical effect

3.3.1.1. Cure rate. Nineteen RCTs[30,31,32,28,35–45,47,50,51,52] showed a favorable effect of simple-needling in cure rate. Figure 4 showed the result of the meta-analysis (RR = 2.29, 95% CI [1.96,2.68], $P < .00001$)with low heterogeneity ($P = .15$, $I^2 = 24\%$), and using fixed effect model.

3.3.1.2. Markedly effective rate. Fourteen RCTs[31–33,35,36,38,39,41,45–47,50–52] tested the markedly effective rate of simple-needling compared to ibuprofen in women with PD, but the meta-analysis result showed no statistical significance (RR = 1.19, 95% CI [0.91, 1.56], $P = .19$). Heterogeneity test $P = .001$, $I^2 = 58\%$, using random effect model. (Fig. 5)

3.3.1.3. Total effective rate. Twenty one RCTs[30–33,35–47,49–52] compared the total effective rate of simple-needling with ibuprofen treatment. The result showed a favorable effect of simple-needling on total effective rate (RR = 1.24, 95% CI [1.19, 1.29], $P < .00001$). Heterogeneity test P = 0.41, I2 = 4%, low heterogeneity, using fixed effect model. (Fig. 6)

3.3.2. VAS score. For the VAS score, 10 RCTs[34,35,36,37,38,40,46,47,48,50] reported it as meta-analysis outcomes liked Figure 7. The result highlighted that simple-needling had a protective effect [Mean Difference = −1.24, 95% CI [-1.92, −0.55], $P = .0004$] with high heterogeneity ($P < .00001$, $I^2 = 95\%$), and using random effect model.

3.3.3. Outcomes of safety. Seven studies[30,33,34,35,46,48,50] reported adverse events, of which 3 studies[30,35,46] had no adverse events and 4 studies[33,34,48,50] had mild adverse events and were properly resolved.

3.3.4. Sensibility analysis. Sensitivity analysis was used for results with high heterogeneity. In all the sensitivity analysis results, the results of the significant efficiency had changed, indicating that the results are unstable, which may be related to different types of needling. The strength and direction of the results of the remaining sensitivity analysis are robust.

3.3.5. Publication bias. The statistically significant outcome indicators in the meta-analysis results were used to evaluate the possibility of publication bias through a funnel chart. The comparison-adjusted funnel plots did not reveal any evidence of apparent asymmetry. (Fig. 8 and Fig. 9)

4. Discussion

4.1. Summary of main findings

This is an up-to-date systematic review and meta-analysis assessing the simple-needling used for PD. "Meta" comes from the Greek meaning "after" or "beyond"; a meta-analysis is an "analytical analysis." [53] In other words, it is a statistical technique that combines the results of different studies on the same subject and is becoming increasingly popular in addressing disparities in clinical research. Thus, a meta-analysis is an objective, quantitative synthesis of research findings,[54] which overcomes the problems of small sample size and insufficient statistical strength by combining the results of previous studies to improve the statistical strength and precision of the estimated effect.[55] This meta-analysis of 23 RCTs, compared the efficacy and safety of simple-needling versus ibuprofen. The results of the meta-analysis showed that simple-needling was superior to ibuprofen treatment in terms of clinical efficacy and improvement of pain symptoms. Four of the 23 studies[28,29,43,45] reported simple-needling had adverse reactions. Most studies did not report adverse events. Severe adverse events of simple-needling were not observed in studies that reported adverse reactions. Most of the adverse events were subcutaneous bleeding or subcutaneous ecchymosis. Those mentioned were mild, and had been properly resolved during the test.

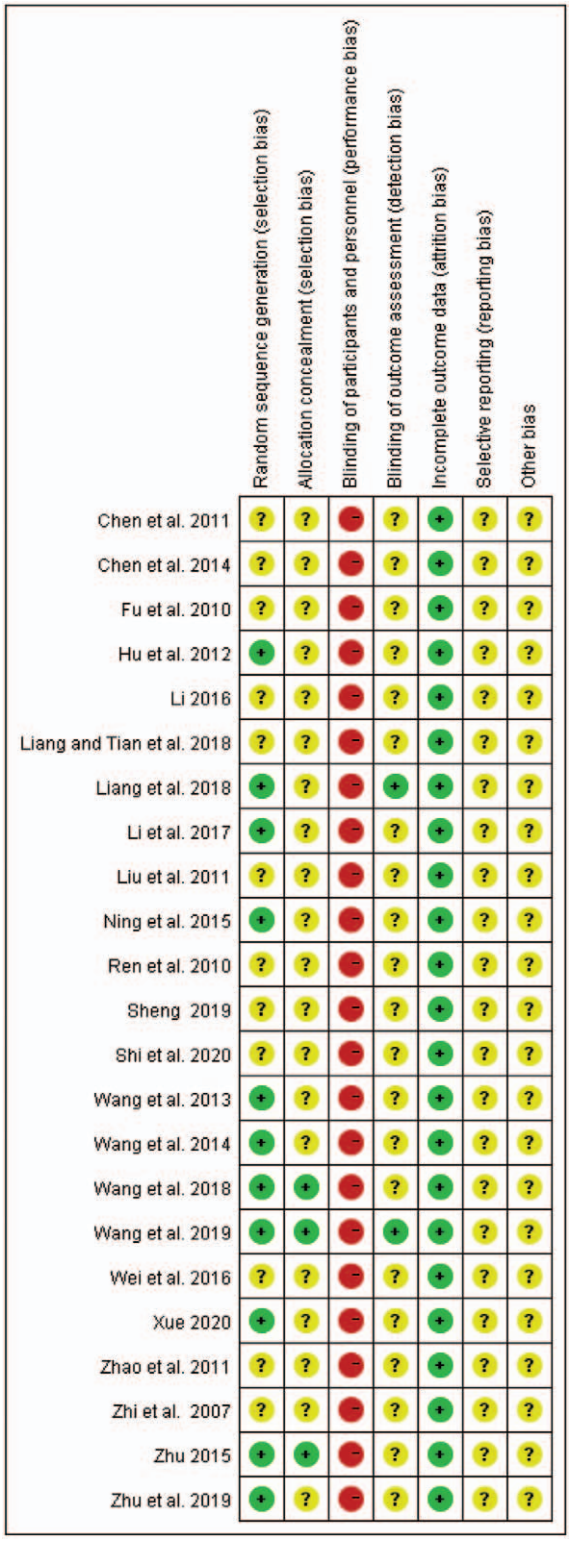

Figure 3. Risk of bias summary of included studies.

4.2. Simple-needling therapy as an evaluation object

Acupuncture treatment has been practiced in China for more than 2 millennia.[56] At the same time, the scientific nature of acupuncture therapy is gradually being recognized in the West.[57] With the development of modern medicine and modern technology, some needling therapies incorporate modern medical theories based on the development of classical meridian therapy, such as the application of electro-acupuncture, superficial needling, wrist-ankle needling, abdominal needling, and other therapies to promote the curative effect of acupuncture and the expansion of acupuncture indications. At present, painful diseases are still one of the main indications of needling, and the main symptom of PD is lower abdomen pain. Therefore, more and more clinical researchers use various needling therapies to treat PD and observe the clinical effects of needling. This study aims to systematically evaluate the clinical effectiveness and safety of simple-needling in the treatment of PD, and to provide a more reliable clinical basis for clinical decision-making.

4.3. Ibuprofen as a controlled drug

PD is a painful disease, and the pathogenesis of PD is currently unanimously recognized that it is mainly related to the increase of PG in the endometrium.[58] NSAIDs are used as first-line drugs for the treatment of most pain diseases, mainly by inhibiting cyclooxygenase, blocking the conversion of arachidonic acid into PG, to achieve anti-inflammatory and analgesic effects.[59] Ibuprofen is the representative drug of NSAIDs, but ibuprofen is prone to allergic reactions of the skin and its accessories and adverse reactions of the digestive system during clinical application,[60] so ibuprofen is used as a controlled drug.

4.4. Strengths and limitations of this review

The strengths of this evaluation system are as follows: Before doing this research, relevant researchers conducted systematic training to ensure the accuracy of the research process. At the same time, 7 electronic databases were searched comprehensively, and medical journals related to non-electronic were searched. This is the report compares the effect of simple-needling and ibuprofen in the treatment of PD, and it provides new evidence and opens new horizons that simple-needling can relieve pain effectively in the treatment of PD and offers advantages in increasing the overall effectiveness. Although there has been a meta-analysis on a related topic,[61] our research differs from the previous meta-analysis in terms of scope and design. First, our study defined in the inclusion criteria that the included studies must have clear diagnostic criteria and efficacy criteria, and the course of treatment was 3 menstrual cycles. Second, although our search strategy is similar, the previous research did not search-related documents after June 2018, which may have a certain impact on the results. Third, regarding the evaluation of clinical efficacy, the previous study only conducted a meta-analysis for the total effective rate, our study not only report it but also report the meta-analysis results of the clinical cure rate. Analysis of the results further evaluated the clinical efficacy of simple-needling. Finally, the previous meta-analysis only evaluated the clinical efficacy of needling in the treatment of PD, but did not evaluate the safety of needling in the treatment of PD.

The limitations of this evaluation system are as follows:

1. Most of the included studies did not mention sample estimation methods, and the sample sizes were small, which may cause heterogeneity between studies.
2. Some of the included RCTs did not describe the method of random sequence generation, which may cause bias in the results.

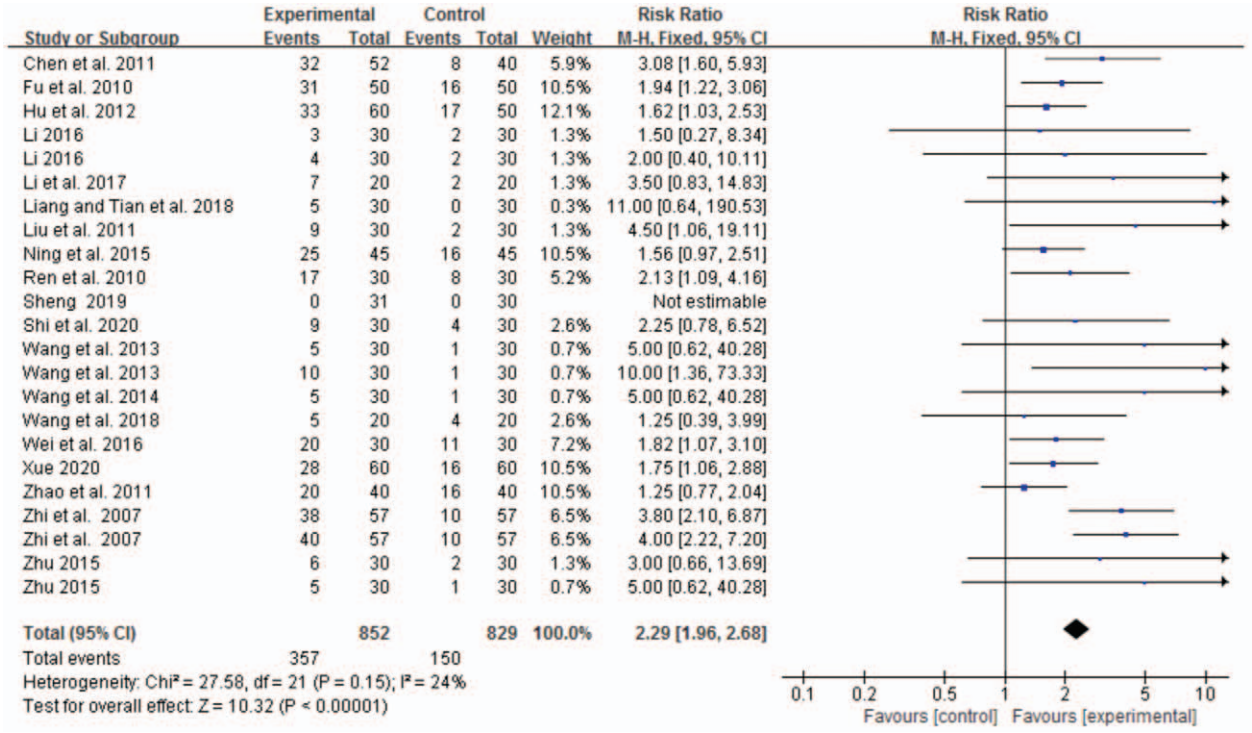

Figure 4. Meta-analysis of cure rate.

3. Allocation concealment was not explained in most studies, which may exaggerate the therapeutic effect.
4. The evaluation of efficacy was mainly based on subjective perception. Insufficient blinding may increase the risk of bias. However, most of the included studies did not describe the implementation of blinding.
5. Given the dropped cases, most studies did not conduct ITT.
6. Although Chinese and English databases were searched, the final included studies were concentrated in China, so the research results may be biased.
7. Most studies only evaluated short-term effects and ignored long-term effects.

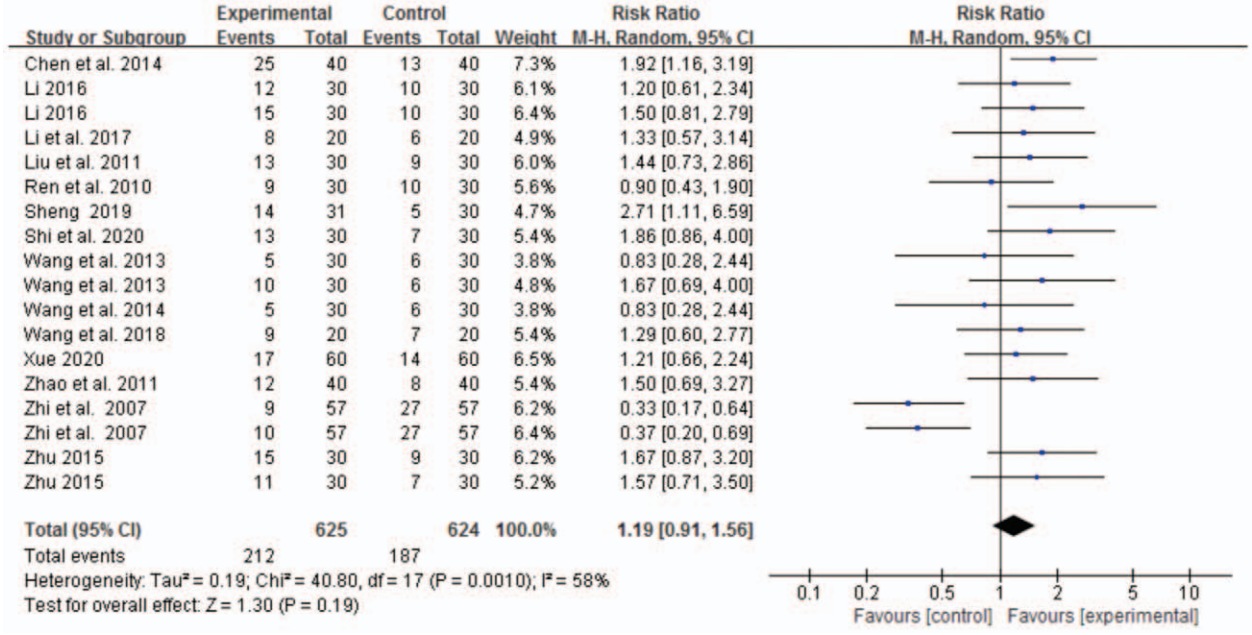

Figure 5. Meta-analysis of markedly effective rate.

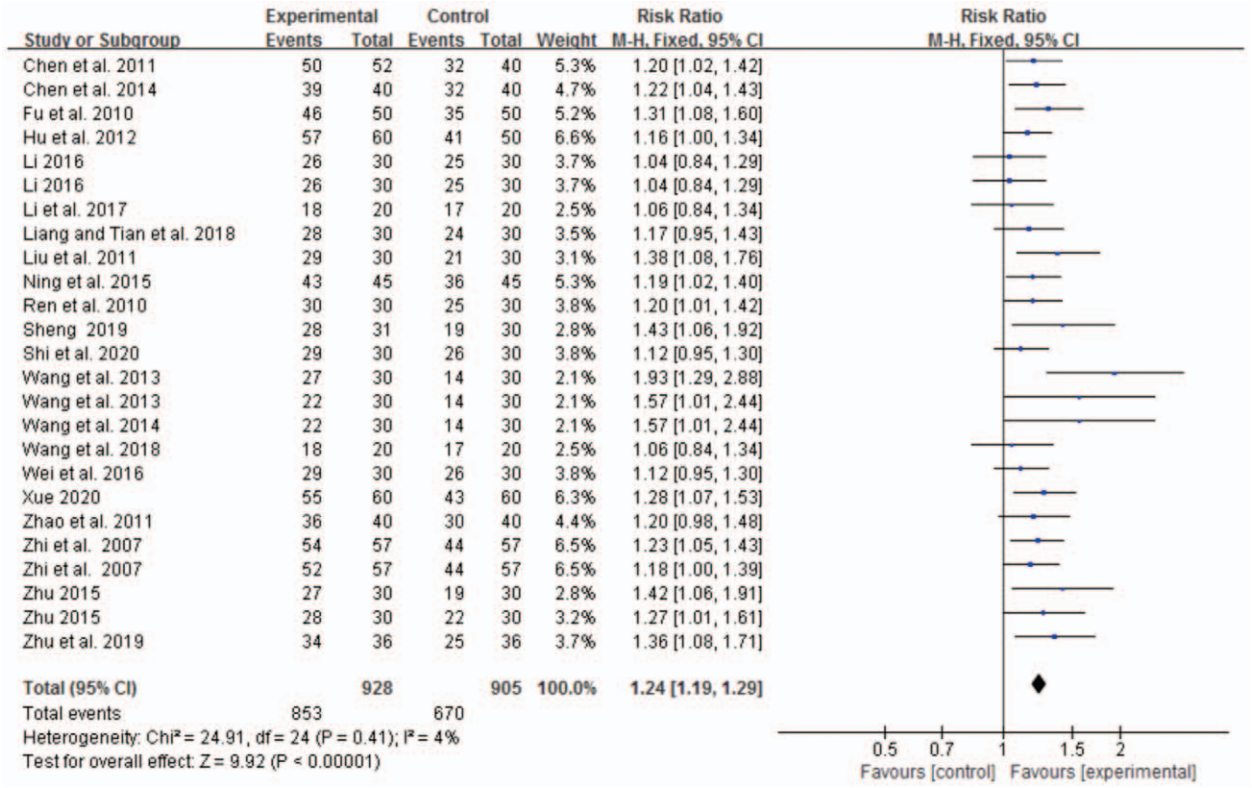

Figure 6. Meta-analysis of total effective rate.

4.5. Direction of future research

According to the limitations we found in our research, we must adopt strict methods to conduct high-quality clinical research in the future. In RCTs, we need to describe the generation of random sequences in detail, implement allocation concealment, and pay attention to the implementation of blinding to ensure the objectivity of the results. At the same time, ITT should be used to reduce the bias of the results for the cases that fall off or discontinue treatment during the research process for some reasons. Finally, researchers should expand the sample size and appropriately select PD patients outside of China for clinical research.

5. Conclusion

The current evidence shows that simple-needling is more effective than ibuprofen in the treatment of PD. It also proves the role of simple-needling in improving VAS. Regarding the safety of simple-needling in the treatment of PD, a small number of studies report the occurrence of safety, so there is not enough evidence to

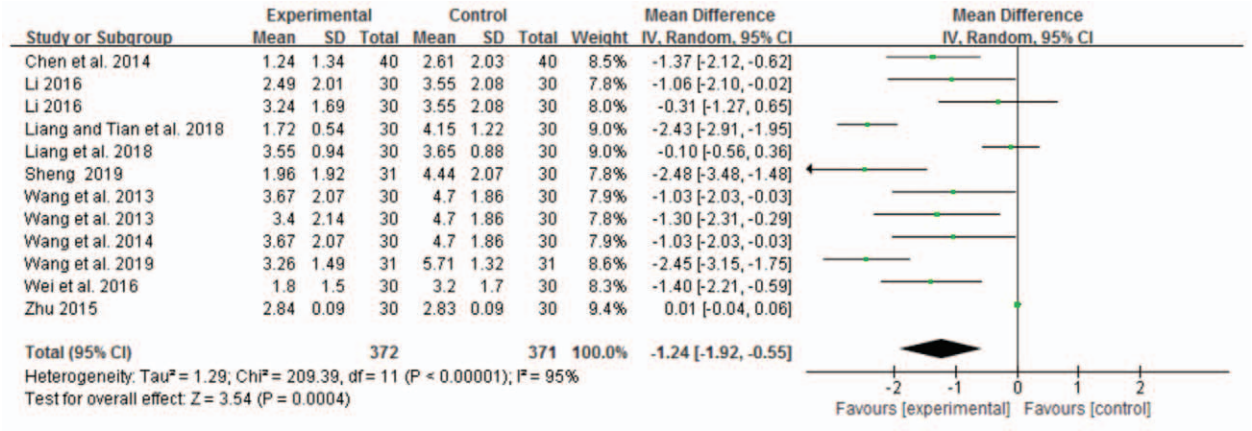

Figure 7. Meta-analysis of VAS score.

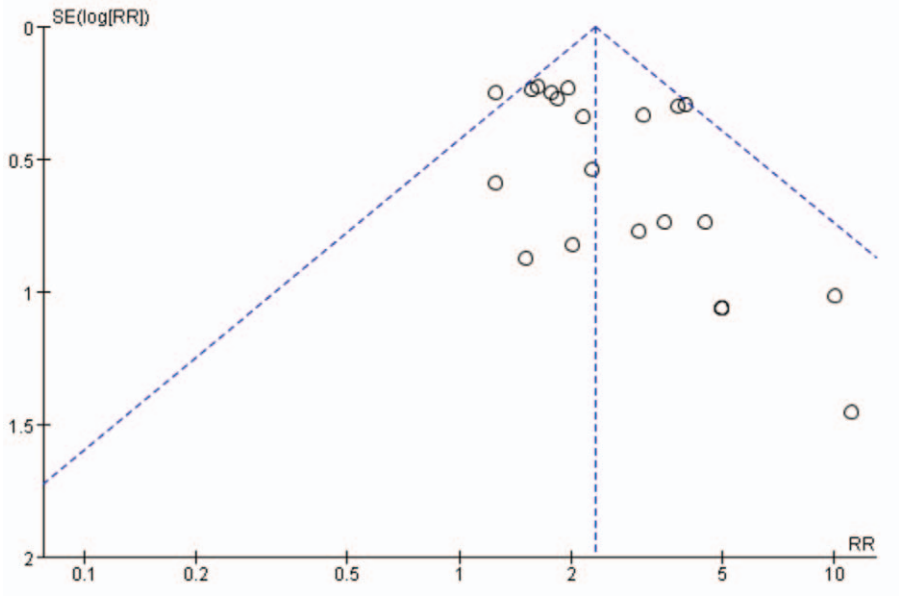

Figure 8. Funnel plot of cure rate.

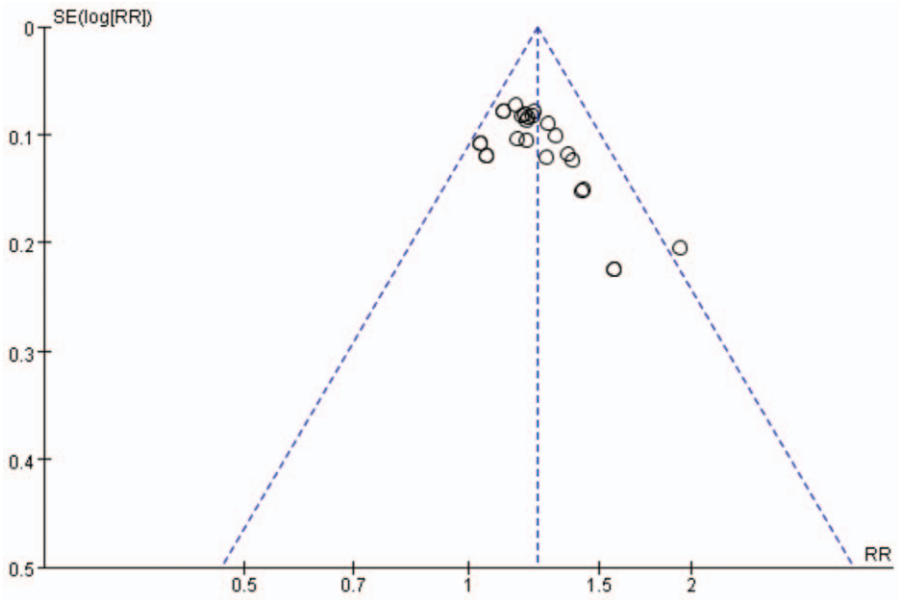

Figure 9. Funnel plot of total effective rate.

support the safety of simple-needling in the treatment of PD. In addition, our results have limitations and require more high-quality RCTs to verify.

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