

Comparative efficacy and safety of NSAIDs-controlled acupuncture in the treatment of patients with primary dysmenorrhoea: a Bayesian network meta-analysis

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Abstract

Background: Acupuncture and non-steroidal anti-inflammatory drugs (NSAIDs) are used frequently to treat primary dysmenorrhoea. However, it is unclear whether this treatment greatly reduces the risk of primary dysmenorrhoea.

Methods: Eight databases were searched up to January 2018. Pair-wise and network meta-analyses were conducted to synthesize data from eligible studies.

Results: Seventeen randomized controlled trials were included. The following acupuncture types showed more efficacy than NSAIDs in reducing primary dysmenorrhoea risk: traditional acupuncture (odds ratio [OR] = 6.70, 95% confidence interval [CI] 2.60–20.0), eye acupuncture (OR = 3.50, 95% CI 1.40–8.90), wrist–ankle acupuncture (OR = 6.00, 95% CI 1.30–32.0), superficial acupuncture (OR = 5.10, 95% CI 1.20–26.0), moxibustion (OR = 7.70, 95% CI 2.90–25.0), electroacupuncture (OR = 23.0, 95% CI 4.80–130), ear acupuncture (OR = 13.0, 95% CI 2.80–100) and abdominal acupuncture (OR = 5.30, 95% CI 2.10–16.0). Surface under the cumulative ranking curve values were traditional acupuncture (53.0%), eye acupuncture (22.0%), wrist–ankle acupuncture (81.5%), superficial acupuncture (50.0%), moxibustion (57.8%), electroacupuncture (99.9%), ear acupuncture (41.6%) and abdominal acupuncture (44.1%).

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Conclusion: Acupuncture is more efficacious than NSAIDs in reducing primary dysmenorrhoea risk. Acupuncture, particularly electroacupuncture, can decrease the risk of primary dysmenorrhoea.

Keywords

Primary dysmenorrhoea, acupuncture, non-steroidal anti-inflammatory drugs, randomized controlled trial, network meta-analysis, electroacupuncture

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Introduction

Primary dysmenorrhoea is characterized by the presence of lower abdominal pain and distension in the lower abdomen before and after menstruation in the absence of organic lesions in the reproductive organs. It is one of the most common gynaecological symptoms and can severely affect quality of life.¹ Primary dysmenorrhoea accounts for more than 90% of dysmenorrhoea, and is most common in adolescence.² Dysmenorrhoea is a common problem and can occur in 50% of menstruating women.³ There are many current approaches to treat dysmenorrhoea, such as oral administration of traditional Chinese medicine, external use of traditional Chinese medicine,⁴ acupuncture⁵ and non-steroidal anti-inflammatory drugs (NSAIDs).^{6,7}

According to Western medicine, primary dysmenorrhoea is associated with increased levels of prostaglandins.⁸ Oral pain relief is often prescribed for dysmenorrhoea symptoms, but they are often ineffective or slow-acting.⁸ NSAIDs are widely used as the first-line therapy for females with dysmenorrhoea.⁷ The traditional Chinese medicine interpretation of primary dysmenorrhoea is stagnation of qi and blood. By improving qi and blood flow, acupuncture can not only reduce symptoms, but also improve the quality of life of dysmenorrhoea patients.⁹

Acupuncture and NSAIDs are commonly used to treat primary dysmenorrhoea. Xu et al. found that acupuncture therapy is more efficacious than NSAIDs in reducing the risk of primary dysmenorrhoea.¹⁰ However, it is unclear whether all types of acupuncture therapy are efficacious in treating primary dysmenorrhoea, and which acupuncture therapies provide the most efficacy in primary dysmenorrhoea treatment. We conducted a network meta-analysis of randomized controlled trials to determine the efficacy and safety of NSAIDs-controlled acupuncture in primary dysmenorrhoea treatment.

Methods

Search strategy

Eligible studies were systematically searched to January 2018 using Medline, Embase, Web of Science, Cochrane Database, Chinese Academic Journals Full-text Database, Chinese Science and Technology Journal Full-text Database, Wanfang Data and Chinese Biomedical Literature Database. The keywords were “Primary Dysmenorrhoea” [MeSH] OR “Menstrual Pains” [MeSH] AND “Acupuncture” [MeSH] OR “Acupuncture Therapy” [MeSH] AND “NSAIDs” [MeSH] OR “Non-Steroidal Anti-Inflammatory Agents”

[MeSH] OR “Anti-Inflammatory Analgesics” [MeSH] OR “Aspirin Like Agents” [MeSH].

Inclusion criteria and data extraction

We only included randomized controlled trials written in English, regardless of whether the authors mentioned specific random allocation methods, randomization distribution schemes, or blinding methods. No restriction was placed on date of publication. Subjects in all trials were diagnosed with primary dysmenorrhoea. All studies focused on the effect of acupuncture compared with NSAIDs on primary dysmenorrhoea.

We input the studies retrieved from the database into EndNote and eliminated duplicate documents. We read the titles and abstracts according to the elements in the PICOS approach (participants, interventions, comparators, outcomes and study design) to conduct preliminary screening, and then read the full text. The data were extracted and evaluated by two staff members, who discussed and resolved any differences. All relevant data were recorded for each study, including first author name, publication time, sample size, age, and intervention measures. Quality evaluation was conducted using the Cochrane risk of bias tool.¹¹

Statistical analysis

The risk of primary dysmenorrhoea in each group was compared using the odds ratios (ORs) and the 95% confidence intervals (95% CIs). A summary effect (pooled OR) was produced for each pair-wise comparison using a meta-analytic approach (fixed-effect model). The validity of the fixed-effect model was assessed by examining study heterogeneity in each pair-wise comparison. The degree of heterogeneity was quantified using Cochran's Q and I²

statistics. If the P value of Cochran's Q test statistic is less than 0.05 or the I² statistic is larger than 50%, this indicates significant heterogeneity among included studies for each pair-wise comparison. As a result, the fixed-effect model may not be appropriate for synthesizing direct evidence and the random-effects model should be used instead.

We conducted a network meta-analysis (Bayesian approach) that included both direct and indirect evidence in the network. Acupuncture types were ranked based on the surface under the cumulative ranking curve (SUCRA) values. Adjuvant treatments with greater SUCRA values are considered preferable. The presence of small study effects or publication bias was visually assessed using funnel plots.

Results

Literature search results

After removing duplicated studies, 955 studies were identified from the eight databases. After reviewing their titles and abstracts, 918 citations were excluded. The remaining 37 citations were assessed in more detail for eligibility by reading the full text. Of these, 1 study was excluded owing to lack of a relevant outcome measure, 11 studies were excluded because of insufficient network connections and 8 studies were excluded owing to a lack of detailed information. A total of 17 studies were used for the final data synthesis. The flow chart of the literature search is shown in Figure 1. The risk of bias of the 17 studies included in this meta-analysis is summarized in Figure 2. The characteristics of the included studies are shown in Table 1.^{12–28} The pattern of evidence in the network is displayed in Figure 3.

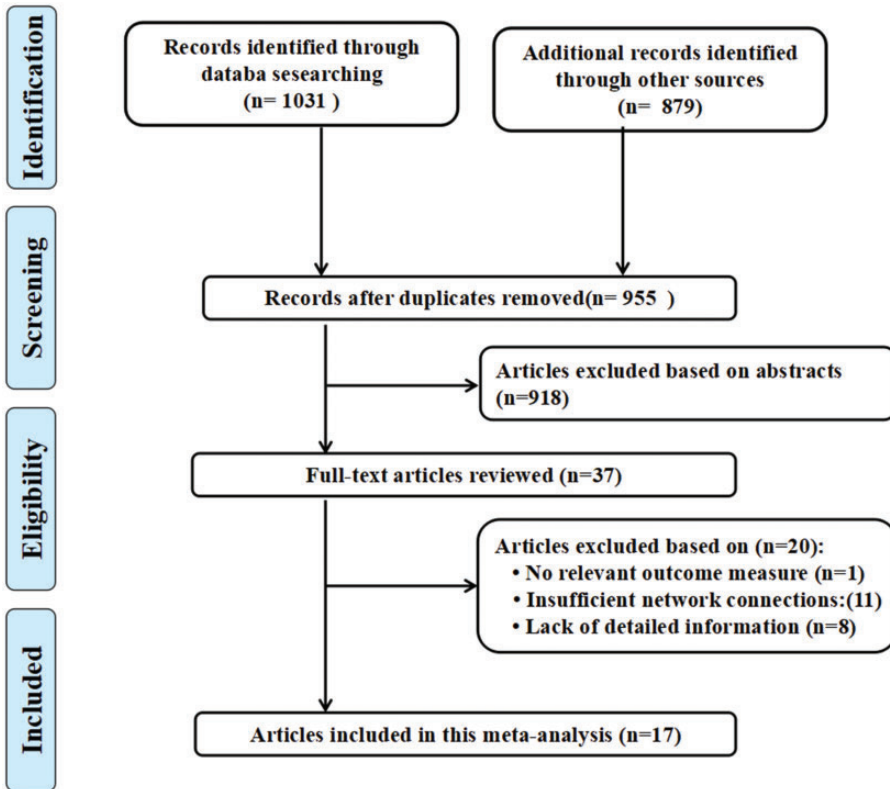


Figure 1. Flow diagram of the study selection process.

Results of pair-wise meta-analysis

Table 2 shows the results of the pair-wise meta-analysis. The following types of acupuncture appeared to show more efficacy than NSAIDs in reducing the risk of primary dysmenorrhoea: traditional acupuncture (OR = 7.10, 95% CI 2.80–21.0), eye acupuncture (OR = 3.90, 95% CI 1.50–9.10), wrist–ankle acupuncture (OR = 5.60, 95% CI 1.30–31.0), superficial acupuncture (OR = 5.10, 95% CI 1.20–24.0), moxibustion (OR = 7.60, 95% CI 2.80–27.0), electroacupuncture (OR = 22.0, 95% CI 4.50–120), ear acupuncture (OR = 13.0, 95% CI 2.70–130), and abdominal acupuncture (OR = 5.50, 95% CI 2.10–16.0). In addition, there was low heterogeneity among studies (P-heterogeneity > 0.05 and $I^2 < 50\%$) (Table 2).

Network meta-analysis

Table 3 shows the results of the network meta-analysis. The following types of acupuncture appeared to show more efficacy than NSAIDs in reducing the risk of primary dysmenorrhoea: traditional acupuncture (OR = 6.70, 95% CI 2.60–20.0), eye acupuncture (OR = 3.50, 95% CI 1.40–8.90), wrist–ankle acupuncture (OR = 6.00, 95% CI 1.30–32.0), superficial acupuncture (OR = 5.10, 95% CI 1.20–26.0), moxibustion (OR = 7.70, 95% CI 2.90–25.0), electroacupuncture (OR = 23.0, 95% CI 4.80–130), ear acupuncture (OR = 13.0, 95% CI 2.80–100), and abdominal acupuncture (OR = 5.30, 95% CI 2.10–16.0).

The corresponding SUCRA values are shown in Figure 4. The corresponding

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cao 2011	+	?	?	?	-	?	?
Chen 2009	+	?	?	?	+	?	?
Hu 2012	+	?	?	?	+	?	?
Ji 2012	+	?	?	?	+	?	?
Jiang 2007	-	?	?	?	+	?	?
Li 2012	+	?	?	?	+	?	?
Li 2012	+	?	?	?	+	?	?
Lin 2012	+	?	?	?	+	?	?
Liu 2011	+	?	?	?	+	?	?
Ren 2013	-	?	?	?	+	?	?
Wang 2005	+	?	?	?	+	?	?
Xing 2011	-	?	?	?	+	?	?
Yang 2009	+	?	?	?	+	?	?
Zhang 2012	+	?	?	?	+	?	?
Zhi 2007	+	?	?	?	+	?	?
Zhu 2010	+	?	?	?	+	?	?
Zhu 2011	+	?	?	?	+	?	+

Figure 2. Risk of bias of the included randomized controlled trials (review authors’ judgments about each risk of bias item for each included study. + indicates low risk; - indicates high risk; ? indicates unclear risk).

rankings based on SUCRA values were as follows: traditional acupuncture (53.0%), eye acupuncture (22.0%), wrist–ankle acupuncture (81.5%), superficial acupuncture

(50.0%), moxibustion (57.8%), electroacupuncture (99.9%), ear acupuncture (41.6%), and abdominal acupuncture (44.1%). The use of acupuncture, particularly electroacupuncture, was significantly associated with a decreased risk of primary dysmenorrhoea.

Publication bias

The comparison-adjusted funnel plots did not reveal any evidence of apparent asymmetry (Figure 5). No significant publication bias was observed.

Discussion

Ancient traditional Chinese medicine literature records that acupuncture can be used to treat dysmenorrhoea by moving the qi and blood and resolving stasis, indicating an early understanding of dysmenorrhoea.²⁹ Clinically, traditional Chinese medicine categorizes the causes of dysmenorrhoea into five types: stagnation of qi and blood, stagnation of liver and dampness, stagnation of cold and dampness, deficiency of liver and kidney, and deficiency of qi and blood. In contrast, Western medicine considers the occurrence of primary dysmenorrhoea to be closely related to the increase of prostaglandin and interleukin.³⁰ The main pathogenesis of dysmenorrhoea is spastic contraction of the uterine smooth muscle, manifested as increased uterine muscle tension, resulting in reduced uterine blood flow and uterine hypoxia-ischaemia.¹ The increase of interleukin causes the spasmodic contraction of the smooth muscle of the uterus and results in dysmenorrhoea.^{30,31} Moreover, dysmenorrhoea is most severe in the first 2 days of menstruation, when the concentration of prostaglandin F2 α (PGF2 α) and PGF2 α /PGE2 increases significantly in the endometrium.³² Acupuncture can greatly reduce PGF2 α /PGE2 in dysmenorrhoea patients,

Table 1. Characteristics of included studies.

Author (year)	No. of Participants	Treatments					Case/n	Age (year)	Case/n	Age (year)	Case/n
		Treatments 1	Age (year)	Treatments 2	Age (year)	Case/n					
Zhang et al. (2012)	90	Traditional acupuncture	13-27	Indometacin	11-25	42/45	11-25	32/45			
Lin et al. (2012)	140	Eye acupuncture	15-30	Ibuprofen	15-30	76/80	15-30	48/60			
Hu et al. (2012)	110	Eye acupuncture	15-30	Ibuprofen	15-29	57/60	15-29	41/50			
Cao (2011)	59	Wrist-ankle acupuncture	15-29	Ibuprofen	20-28	25/29	20-28	16/30			
Zhi (2007)	120	Superficial acupuncture	19.60 ± 3.20	Indometacin	18.93 ± 2.60	56/60	18.93 ± 2.60	45/60			
Ren (2013)	80	Moxibustion	16-28	Ibuprofen	16-27	36/40	16-27	34/40			
Zhu et al. (2010)	102	Moxibustion	18-26	Indometacin	19-25	47/51	19-25	39/57			
Li (2012)	60	Electroacupuncture	19-30	Fenbid	19-25	24/30	19-25	5/30			
Wang et al. (2005)	58	Ear acupuncture	16-28	Indometacin	15-24	29/30	15-24	18/28			
Yang (2009)	72	Abdominal acupuncture	14-28	Indometacin	13-27	34/36	13-27	29/36			
Chen et al (2006)	58	Abdominal acupuncture	16-28	Indometacin	15-24	29/30	15-24	18/28			
Liu et al. (2011)	80	Moxibustion	21.22 ± 5.86	Fenbid	20.96 ± 6.12	39/40	20.96 ± 6.12	29/40			
Zhu et al. (2011)	40	Traditional acupuncture	17-28	Indometacin	18-27	19/20	18-27	16/20			
Li et al. (2012)	200	Traditional acupuncture	13-30	Ibuprofen	14-35	96/100	14-35	77/100			
Jiang (2007)	68	Ear acupuncture	19.35 ± 4.33	Indometacin	20.55 ± 4.51	33/34	20.55 ± 4.51	29/34			
Xing (2011)	114	Abdominal acupuncture	15-27	Indometacin	16-32	55/60	16-32	42/54			
Ji et al. (2012)	60	Moxibustion	22 ± 3	Indometacin	22 ± 2	29/30	22 ± 2	25/30			

effectively inhibit uterine smooth muscle spasmodic contraction, and increase uterine blood flow. This reduces local ischaemia and hypoxia and generates an analgesic effect.³³

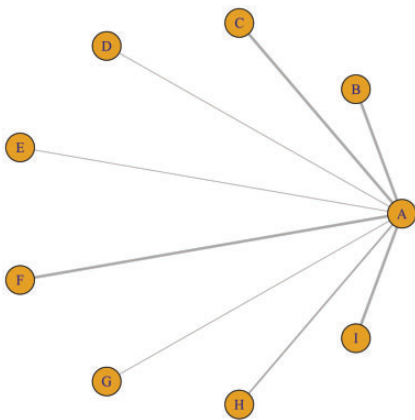


Figure 3. Network of randomized controlled trials comparing different acupuncture therapies for primary dysmenorrhoea treatment. The thickness of the connecting lines represents the number of trials between each comparator, and the size of each node corresponds to the number of subjects who received the same pharmacological agent (sample size). (A: Non-steroidal anti-inflammatory drugs [NSAIDs]; B: Traditional acupuncture; C: Eye acupuncture; D: Wrist–ankle acupuncture; E: Superficial acupuncture; F: Moxibustion; G: Electroacupuncture; H: Ear acupuncture; I: Abdominal acupuncture).

A previous meta-analysis of 42 randomized controlled trials reported an association between acupuncture and dysmenorrhoea risk, and found that acupuncture was effective in treating primary dysmenorrhoea.⁵ Furthermore, Yang et al. found that acupuncture therapy is more efficacious than NSAIDs in reducing the risk of primary dysmenorrhoea.¹⁰ However, no previous studies have examined whether all acupuncture therapy methods are efficacious in treating primary dysmenorrhoea, or have clarified which type of acupuncture therapy shows most efficacy in primary dysmenorrhoea treatment.

In this network meta-analysis, we compared the efficacy of acupuncture therapies for primary dysmenorrhoea and examined which acupuncture therapy showed most efficacy for primary dysmenorrhoea compared with NSAIDs. The results suggest that traditional acupuncture, eye acupuncture, wrist–ankle acupuncture, superficial acupuncture, moxibustion, electroacupuncture, ear acupuncture, and abdominal acupuncture are more efficacious than NSAIDs in reducing the risk of primary dysmenorrhoea, and that the use of acupuncture, particularly electroacupuncture, is significantly associated with a decreased risk of primary dysmenorrhoea. The SUCRA ranking scheme ranked wrist–ankle acupuncture lower than electroacupuncture. The use of

Table 2. Summary odds ratios of acupuncture and heterogeneity for each direct comparison.

Comparison	OR (95% CI)	P-heterogeneity	I-squared	Tau-squared
Traditional acupuncture vs. NSAIDs	7.10 (2.80, 21.0)	0.697	<0.01%	<0.001
Eye acupuncture vs. NSAIDs	3.90 (1.50, 9.10)	0.790	<0.01%	<0.001
Wrist–ankle acupuncture vs. NSAIDs	5.60 (1.30, 31.0)	0.723	<0.01%	<0.001
Superficial acupuncture vs. NSAIDs	5.10 (1.20, 24.0)	0.146	5.90%	<0.001
Moxibustion vs. NSAIDs	7.60 (2.80, 27.0)	0.811	<0.01%	<0.001
Electroacupuncture vs. NSAIDs	22.0 (4.50, 120)	0.887	<0.01%	<0.001
Ear acupuncture vs. NSAIDs	13.0 (2.70, 130)	0.730	<0.01%	<0.001
Abdominal acupuncture vs. NSAIDs	5.50 (2.10, 16.0)	0.814	<0.01%	<0.001

OR: odds ratio; CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs.

Table 3. Network meta-analysis comparisons.

	NSAIDs	Traditional acupuncture	Eye acupuncture	Wrist-ankle acupuncture	Superficial acupuncture	Moxibustion	Electroacupuncture	Ear acupuncture	Abdominal acupuncture
NSAIDs	1	0.15 (0.05,0.40)	0.29 (0.11,0.72)	0.16 (0.03,0.80)	0.19 (0.04,0.84)	0.13 (0.04,0.36)	0.04 (0.01,0.21)	0.08 (0.01,0.37)	0.19 (0.06,0.51)
Traditional acupuncture	6.70 (2.60,20.0)	1	2.00 (0.51,8.00)	1.10 (0.15,7.40)	1.30 (0.20,7.70)	0.86 (0.19,3.60)	0.29 (0.04,2.00)	0.51 (0.05,3.40)	1.30 (0.29,5.20)
Eye acupuncture	3.50 (1.40,8.90)	0.51 (0.12,2.10)	1	0.57 (0.08,3.60)	0.64 (0.11,4.00)	0.44 (0.10,1.80)	0.15 (0.02,0.95)	0.26 (0.03,1.70)	0.65 (0.15,2.60)
Wrist-ankle acupuncture	6.00 (1.30,32.0)	0.91 (0.14,6.60)	1.70 (0.28,12.0)	1	1.20 (0.13,11.0)	0.76 (0.10,5.60)	0.25 (0.02,2.60)	0.45 (0.03,4.90)	1.10 (0.16,7.40)
Superficial acupuncture	5.10 (1.20,26.0)	0.77 (0.12,5.20)	1.50 (0.26,9.90)	0.80 (0.09,8.10)	1	0.64 (0.10,4.30)	0.21 (0.02,2.10)	0.38 (0.03,3.80)	0.95 (0.15,6.10)
Moxibustion	7.70 (2.90,25.0)	1.10 (0.27,5.50)	2.20 (0.56,10.0)	1.30 (0.18,9.60)	1.50 (0.24,11.0)	1	0.34 (0.05,2.50)	0.58 (0.06,4.50)	1.50 (0.32,6.90)
Electroacupuncture	23.0 (4.80,130)	3.30 (0.48,24.0)	6.50 (1.10,49.0)	3.80 (0.37,41.0)	4.10 (0.46,40.0)	2.80 (0.39,22.0)	1	1.70 (0.13,17.0)	4.20 (0.61,30.0)
Ear acupuncture	13.0 (2.80,100)	2.00 (0.29,20.0)	3.80 (0.57,35.0)	2.20 (0.21,29.0)	2.60 (0.27,35.0)	1.60 (0.22,16.0)	0.53 (0.05,7.20)	1	2.40 (0.34,29.0)
Abdominal acupuncture	5.30 (2.10,16.0)	0.79 (0.19,3.50)	1.60 (0.41,6.60)	0.85 (0.13,6.20)	1.00 (0.16,6.60)	0.70 (0.14,3.30)	0.23 (0.03,1.60)	0.39 (0.04,2.90)	1

NSAIDs: non-steroidal anti-inflammatory drugs. Italicized values are significant at $P < 0.05$.

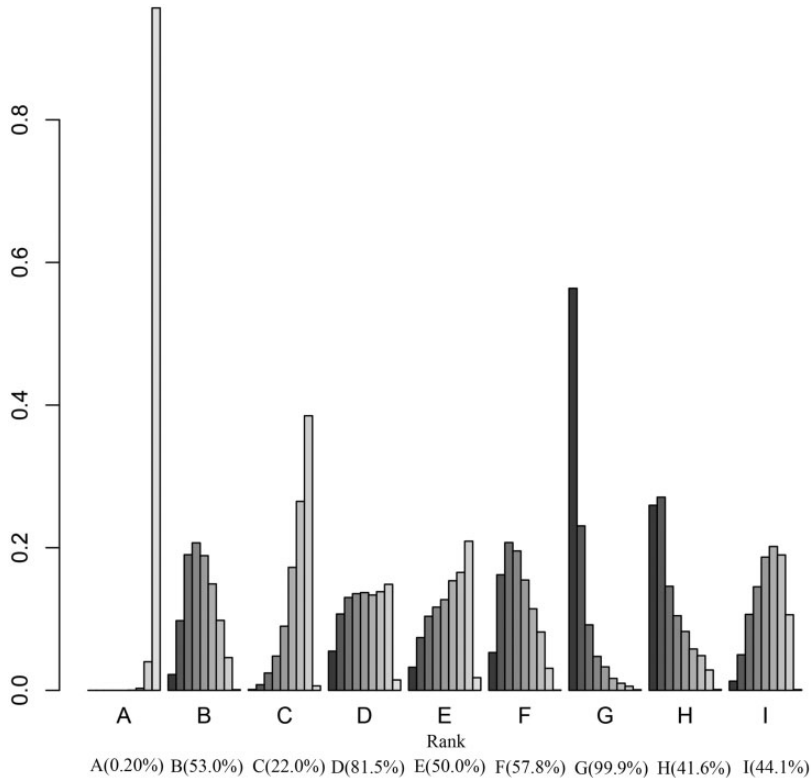


Figure 4. Surface under the cumulative ranking curve (SUCRA), expressed as percentages, ranking the therapeutic effects and safety of treatments for primary dysmenorrhoea. For efficacy and safety assessment, the pharmacological agent with the highest SUCRA value is assumed to be the safest, most efficacious treatment. (A: Non-steroidal anti-inflammatory drugs [NSAIDs]; B: Traditional acupuncture; C: Eye acupuncture; D: Wrist–ankle acupuncture; E: Superficial acupuncture; F: Moxibustion; G: Electroacupuncture; H: Ear acupuncture; I: Abdominal acupuncture).

clinical syndromes to diagnose patients means that traditional Chinese medicine can tailor the prescription to the patient, and a good curative effect is often obtained.

Acupuncture is simple, efficient, and safe, and plays an important role in the treatment of primary dysmenorrhoea. Electroacupuncture is one of the most widely used acupuncture methods in clinical practice. Endogenous opioid receptors mediate the analgesic effects of electroacupuncture.³⁴ In one study, electroacupuncture was used to stimulate the acupuncture point SP6, which resulted in an increase of beta-

endorphins in the rat uterus and consequent analgesia.³⁴ Hypoimmunity is a typical manifestation of primary dysmenorrhoea.³⁵ Electroacupuncture can lead to the release of interleukin-1 and interleukin-6 and increase the activity of natural killer cells in rats with primary dysmenorrhoea.³⁶ Additionally, electroacupuncture can effectively improve blood flow in the uterus of patients with dysmenorrhoea, reducing local ischaemia and hypoxia.³⁷

This meta-analysis had some limitations. The statistical tests used to examine heterogeneity in the randomized controlled trials lacked power, and there was limited

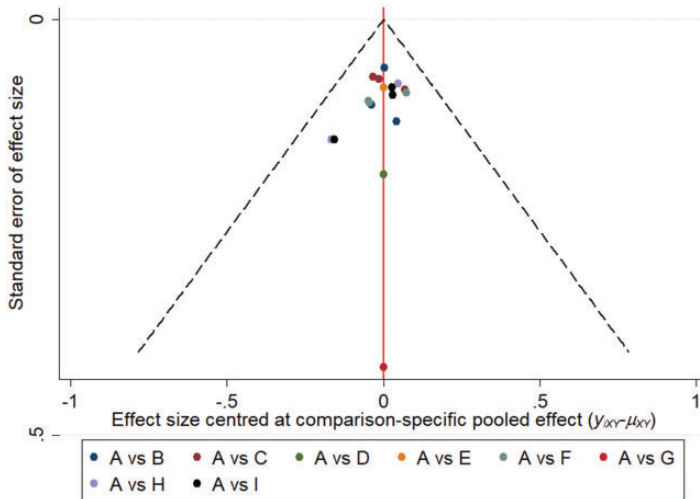


Figure 5. Comparison-adjusted funnel plot for the network meta-analysis. The red line suggests the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors represent different comparisons. (A: Non-steroidal anti-inflammatory drugs [NSAIDs]; B: Traditional acupuncture; C: Eye acupuncture; D: Wrist-ankle acupuncture; E: Superficial acupuncture; F: Moxibustion; G: Electroacupuncture; H: Ear acupuncture; I: Abdominal acupuncture).

evidence of a dose-dependent association between acupuncture therapy and dysmenorrhoea; therefore, we can have only limited confidence in the study findings. Second, standardized treatment methods were not used across the trials. The difference between trials means that the results should be interpreted with caution. Third, the study durations were short and the participants may not be representative of the general population. Fourth, these findings may not be generalizable to other groups of patients, as randomized controlled trials tend to exclude some participants. Fifth, the overall study sample sizes were small, and the overall quality of acupuncture and moxibustion treatment was not high, which may have affected the evaluation results.

Our findings indicate that acupuncture is more efficacious than NSAIDs in reducing the risk of primary dysmenorrhoea. The use of acupuncture, particularly electroacupuncture, seems to be strongly associated with a decreased risk of primary

dysmenorrhoea. Future research requires large-scale and ongoing trials to validate the effect identified in this meta-analysis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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