Efficacy of non-pharmacological interventions for primary dysmenorrhoea: a systematic review and Bayesian network meta-analysis

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Abstract

Objectives To assess the relative benefits of various non-pharmacological interventions on treating primary dysmenorrhoea within a network meta-analysis.

Study design Systematic review and Bayesian network meta-analysis.

Inclusion criteria Randomised controlled trial involving patient with primary dysmenorrhoea and received non-pharmacological interventions.

Data sources Four databases (Medline, Embase, Cochrane Library and Web of Science) were searched from inception to October first, 2022.

Risk-of-bias (RoB) assessment RoB 2.0 assessment tools was used to assess the risk of bias in the included studies.

Synthesis of results Conventional meta-analysis was conducted by pairwise comparison between non-pharmacological therapy and control treatment. The Bayesian network meta-analysis was conducted by the Aggregate Data Drug Information System Software based on the consistency or inconsistency model, and rank probability was used to indicate the priority of non-pharmacological therapy.

Results 33 studies involving eight non-pharmacological interventions were included. With regard to conventional meta-analysis, we selected Visual Analogue Scale (VAS) as primary outcome to evaluate the pain intensity. The result showed that eight interventions (Exercise, Herb, Acupuncture, Aromatherapy, Transcutaneous Electrical Nerve Stimulation, Topical heat, Acupressure, Yoga) displayed positive effect on reduction of menstrual pain compared with placebo or no treatment. A Bayesian network meta-analysis revealed that exercise −3.20 (95% CI −4.01 to −2.34), acupuncture −2.90 (95% CI −3.97 to −2.85) and topical heat −2.97 (95% CI −4.66 to −1.29) probably resulted in a reduction in pain intensity (VAS).

Conclusions Non-pharmacological interventions may result in a reduction or slight reduction in pain intensity compared with no treatment or placebo. Specifically, exercise and acupuncture are considered as potentially effective non-pharmacological treatments in short-term treatment. Indeed, larger and better methodological quality research is needed.

Trial registration number CRD42022351021.

Introduction

Primary dysmenorrhoea (PD) is defined as cramping pain in the lower abdomen that occurs before or during menstruation without identifiable pelvic pathology.1 Dysmenorrhoea is one of the most common problems of adolescents and mature women, whose prevalence ranges from 16.8% to 81%, with rates as high as 90% having been reported.2 PD is usually accompanied by a series of physical symptoms including headaches, dizziness, fatigue and sweating.3 It is noteworthy that the severity of symptoms obviously influence quality of life (QoL), which is the reason why it call our attention.4

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Management of primary dysmenorrhoea mainly focus on western medicines; however, side effect of non-steroidal anti-inflammatory drugs constrains its usage in clinical practice. Non-pharmacological therapies are considered as beneficial supplement to medicine management, due to its lower side effect and applicability.

⇒ Lack of comprehensive synthesis and analysis on evidence regarding the efficacy of non-pharmacological therapy.

WHAT THIS STUDY ADDS

⇒ Non-pharmacological therapy exerts positive effect on the pain reduction of primary dysmenorrhoea. Specifically, exercise is potentially the most effective non-pharmacological intervention in short-term (1–3 menstrual cycles) application.

⇒ The quality of most evidence is not high, and the methodology remain to be improved.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our research provides valuable suggestion for the guidance about non-pharmacological intervention in primary dysmenorrhoea management, and promote the further large-scale investigation on the non-pharmacological intervention in the future.

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According to previous research, PD is considered as the outcome of abnormal prostaglandin (PGs) release which leads to myometrial hypercontractility, as well as insufficient oxygen supply on uterus muscles. In addition, unhealthy lifestyle such as dietary habit and other negative factors also contribute to outbreak of PD.

The basic goal of treatment is minimising the negative impact of PD, specifically including reduction of pain intensity, relief of somatic symptoms and improvement on the QoL. Excessive production and release of PGs during menstruation by the endometrium are the main pathogenesis of dysmenorrhoea, indicating restraint of PGs discharge effectively decrease the intrauterine pressure and hypercontractility. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first line of the pharmacological treatments in PD consensus guideline. However, the concomitant side effects could not be neglected. Convincing evidences showed that long-term intake of NSAIDs will cause higher risk of cardiovascular disease incidence.

Non-pharmacological therapy is composed of various non-invasive or minimal invasive treatments, such as acupuncture, acupressure, exercise, aromatherapy, TENS and herb remedy. Recently, non-pharmacological therapy yields remarkable efficacy in clinical practice, and are widely proved by previous research. Besides, non-pharmacological therapy can avoid side-effect induced by NSAIDs. Several review and meta-analyses have evaluated the efficacy of non-pharmacological interventions on treating PD. A 2016 Cochrane review of 42 randomised controlled trial (RCT) provided preliminary evidence for demonstrating acupuncture and acupressure are effective in treatment, even the quality of research is relatively low. Another systematic review of 27 trials regarding acupuncture reported promising result in treating PD compared with placebo intervention. In spite of effectiveness of individual non-pharmacological therapy being preliminarily verified, the comprehensive review and analysis of collective non-pharmacological therapies are needed.

Network meta-analysis (NMA) is a statistical method that enables synthesis of both direct and indirect comparison within a multitreatment analytic framework, and it allows assessment and rank priority of multiple interventions. Therefore, our analysis aim to assess the clinical efficacy of currently available non-pharmacological treatment by network, thus providing optimal therapeutic strategy for PD management.

Method
We registered this review prospectively in PROSPERO (CRD42022351021). Institutional review board approval was not required as this study did not include individual patient data. The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement: an updated guideline for reporting systematic reviews.

Inclusion criteria and outcome
We included treatment options recommended by evidence-based guidelines on the management of PD: acupuncture, acupressure, exercise, massage, topical heat, aromatherapy, TENS, herb (ginger, cinnamon and fennel extract), yoga, spinal manipulation and moxibustion. Eligible studies had to meet the following criteria: (1) the study was RCT; (2) the included subject were diagnosed with PD; (3) the included interventions were constrained within non-pharmacological therapy; (4) control treatment was sorted as no-treatment or placebo; (5) the visual analogue scale (VAS) was used as primary outcome; (6) the study adopted head-to-head intervention (eg, acupuncture vs acupressure).

The exclusion criteria were as follows: (1) case report, plot study or non-randomised trial; (2) the research data were incomplete; (3) non-English article; (4) the studies adopted mixed intervention (eg, acupuncture plus moxibustion) in experimental group.

Primary outcome was the VAS used to measure pain intensity. The standard of VAS was normalised to 0–10. Measurement of time point was set on one menstrual cycle after initiation of intervention.

Information sources
We searched Medline via PubMed interface, Embase via Elsevier interface, the Cochrane Central Register of Controlled Trials via Cochrane Library, Web of Science via Clarivate and the search period was set from inception to 1 October 2022. First, through inputting all related words of non-pharmacological intervention in the Mesh Database of NCBI, the Mesh Term and Entry Terms were identified. If the search page displayed more than one Mesh Term, we would consider to use one of or several item among them. After primary establishment of search term, we screened it into all interface to identify search strategy. Truncation was used and redundant Entry Term was deleted to simplify the search strategy. Jianpeng Huang was responsible for developing the search strategy. Xinyu Hao was responsible for selecting the search term and management of the search result in each database, and Jianhua Liu was responsible for examining the process and format of strategy. The detailed search terms and retrieval records were shown in the online supplemental table S3. PRISMA-S which evaluated the quality of search strategy was presented in the online supplemental table S2.

Selection of studies and data extraction
Two reviewers respectively examined all abstracts and full text, with disagreements resolved by discussion. We used standardised forms of previous reviews to extract data on author, publication information, trial design, patients, characteristics, type of intervention, duration and primary outcomes at interested time point. Disagreements were resolved through discussion or with assistance from a third reviewer, if necessary.

Risk-of-bias assessment
Two reviewers independently assessed the risk of bias of the included trials. We used the following updated version of ROB 2.0 assessment tools recommended by the Cochrane Collaboration, which collectively encompasses five domains: randomisation process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. For each study, the items were classified as high risk, low risk or medium (some concern) risk.

Data synthesis
Pairwise meta-analysis
Direct pairwise meta-analysis was conducted by Review Manager V5.0. for continuous outcomes. VAS was the only outcome measure for the meta-analysis, and means±SD was used to assess and calculate the effect size of interventions. The heterogeneity was assessed by the I² statistic, which was deemed significant heterogeneity if p<0.05 or I²>50%. If I²<50%, the random-effect model was selected to calculate the effect size. Otherwise, the data were pooled with the fixed-effect model to ensure model...
robustness. Additionally, each pairwise comparison involved at least two studies.

**Network meta-analysis**

We conducted NMA compromising multiple treatment comparisons in a Bayesian framework and obtained the pooled estimates through the Markov chain Monte Carlo method. The NMA was performed by Aggregate Data Drug Information System V.1.16.8.\(^{15}\)

First, in order to estimate effect size (MD and 95% CIs) of included interventions, we judged the selection of consistency or inconsistency model according to result of node-splitting analysis. If node-splitting analysis showed no relevant inconsistency of the evidence, the consistency model would be used to estimate the ranking probability in the network. Otherwise, the inconsistency model would be applied. Second, in order to identify the superiority of the interventions, we estimated the probability of included interventions, which expressed the percentage of effectiveness of intervention that could rank first without uncertainty.\(^{16}\) Third, convergence was assessed by the Brooks-Gelman-Rubin method, which compared within-chain and between-chain variance to calculate the Potential Scale Reduction Factor (PSRF). A PSRF closed to 1 indicates approximate convergence has been reached. Model convergence was deemed acceptable if the PSRF value was less than 1.2.\(^{17}\)

**Inconsistency**

In NMA, due to the more complex evidence structure, we would assess inconsistency of evidence. In addition to heterogeneity within a comparison, inconsistency might even occur with normal meta-analysis, but could only be detected using a NMA.

Node-splitting analysis was an alternative method to assess inconsistency in NMA. It assessed whether direct and indirect evidence on a specific node (the split node) were in agreement. Then, we conducted node-splitting analysis to evaluate the inconsistency of each comparison, specifically the p value in each comparison. P value of the node-splitting analysis exceeding 0.05 indicated no significant consistency. Therefore, consistency model was selected and vice versa.\(^{18}\)

**Grading the certainty of evidence**

The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess the certainty of the evidence in pairwise comparison.\(^{19}\) To evaluate the confidence in the results of NMA, an approach had been developed and recently refined which was called Confidence In Network Meta-Analysis (CINeMA).\(^{20}\) It considered six domains: (1) within-study bias, (2) reporting bias (referring to publication and other reporting bias), (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence. CINeMA makes judgments at three levels (no concerns, some concerns or major concerns) in each domain. Judgments across domains could be summarised into confidence rating of four levels (high, moderate, low, very low) for each relative treatment effect.

**Result**

**Study selection and characteristics of included trials**

Figure 1 showed PRISMA flow diagram for the selection of randomised trials in PD. We totally imported 1557 records to ENDNOTE software, and checked the duplication (534 records). After removing the duplicate records, we reviewed the title and abstract of the rest of 1023 records, subsequently 909 records were discarded. Among the screened 114 studies, we viewed the full text and 81 studies did not meet the inclusion criteria. Specifically, 3 studies adopted mixed treatments (eg, massage plus acupuncture),\(^{21–23}\) 20 studies lack of sufficient statistical data, 8 trials were head-to-head interventions (eg, acupuncture vs acupressure), outcome measure in 27 studies were unrelated to the present study (eg, NRS), 9 trials adopted unrelated intervention (eg, homeopathic remedy) and 7 trials were non-RCT. Finally, 33 trials with 2826 patients were eligible and contributed to the NMA. The network map of VAS showed comparisons of aromatherapy and acupuncture were frequent, whereas comparisons of yoga and topical heat were rarely identified. The network structure is shown in figure 2. Three trials investigated acupuncture (116 patients),\(^{24–26}\) 6 trials acupressure (427 patients),\(^{27–31}\) 4 trials evaluated exercise (419 patients),\(^{32–36}\) 3 trials yoga (196 patients),\(^{37–39}\) 3 trials TENS (256 patients),\(^{40–42}\) 2 trials topical heat (236 patients),\(^{43–44}\) 4 trials evaluated Aromatherapy (421 patients)\(^{45–47}\) and 5 trials herb including ginger, cinnamon and fennel extract (371 patients).\(^{48–52}\) Additionally, three trials was head-to-head design (ie, exercise vs aromatherapy, exercise vs ginger, acupuncture vs acupressure,).\(^{53–55}\) Main characteristics of the included publications and trials were presented in table 1.

**Risk of bias among included studies**

Online supplemental figure 1 showed the result of the risk of bias in the included studies. In total, the studies included in analysis displayed a range of low-to-high risk of biases. Among 33 trials, 32 (96.7%) reported adequate randomisation such as computer-generated random numbers or random number tables. Twenty-seven (81.8%) trials adequately concealed treatment allocation, 8 (24.2%) reported double-blind of patients and 5 (15.2%) conducted analysis of the intention-to-treat principle.\(^{1,24,35,39,42}\) In the process of assessment, we discovered several non-specific factors that could influence the result of bias. Specifically, due to the characteristics of non-pharmacological interventions, it was hard to blind both the patients and the researcher.

Overall bias distribution were as follows: low risk 14 trials (42.4%), some concern 17 trials (51.5%), high risk 2 trials (6.1%), which primarily lack of blinding and had great risk of missing outcome data.

**Pairwise meta-analysis**

The results of conventional pairwise meta-analysis between non-pharmacological interventions and control treatment (placebo or no treatment) were as followed: acupuncture (n=116, MD=−3.09, 95% CIs −4.82 to −1.37, I²=89%), acupressure (n=437, MD=−1.35, 95% CIs −1.70 to −0.99, I²=8%), aromatherapy (n=501, MD=−2.13, 95% CIs −2.80 to −1.45, I²=79%), exercise (n=499, MD=−3.25, 95% CIs −3.93 to −2.56, I²=87%), TENS (n=256, MD=−2.36, 95% CIs −3.76 to −0.95, I²=87%), Herb (n=331, MD=−2.64, 95% CIs −3.28 to −2.00, I²=86%), Topical heat (n=236, MD=−2.59, 95% CIs −3.26 to −1.92, I²=83%), yoga (n=196, MD=−1.08, 95% CIs −1.33 to −0.82, I²=80%) displayed positive effect on reduction of menstrual pain. The forest plots of acupuncture and exercise were respectively presented at figure 3 and figure 4.

**Inconsistency and convergence**

The result of node-splitting analysis was presented in online supplemental table S4. The result of node-splitting analysis was comprised of 14 arms, in which the p value of node-splitting analysis was over 0.05, exhibiting no statistically significant inconsistency. Therefore, consistent model was selected to estimate the effect size. As for the convergence, PSRF in all comparisons were
Efficacy and rank probability of non-pharmacological interventions by the Bayesian NMA

Overall, we evaluated the rank probability of included interventions based on the consistency model, which aggregate relative estimate effect within the network. The relative effect size of consistency model was detailed in supplementary appendix (online supplemental table S6).

As for the rank probability of all intervention, the network map collectively analysed 10 interventions, including 8 active intervention and 2 control interventions (no treatment and placebo). Overall, eight interventions displayed positive effect on reduction of menstrual pain compared with placebo or no treatment. Specifically, exercise −3.20 (95% CI −4.01 to −2.34), acupuncture −2.90 (95% CI −3.97 to −2.85) and topical heat −2.97 (95% CI −4.66 to −1.29) probably resulted in a reduction in pain intensity (VAS), while acupressure −1.73 (95% CI −2.56 to −0.90) may result in a slight reduction in VAS. Online supplemental figure S4 presented the rank probability about the efficacy of different non-pharmacological interventions on pain intensity (VAS) reduction. The results revealed that exercise had the highest probability to approaching 1.00, indicating approximate convergence has been reached.
be ranked 1 (30.0%), followed by topical heat (26.0%), acupuncture (16.0%), TENS (13.0%), herb (11.0%) and aromatherapy (4.0%). The certainty of evidence in NMA varied from moderate to very reliable.

**Publication bias**

The result of comparison-adjusted funnel plot showed relatively symmetry around the zero line (pooled effect size), which indicated studies were equally distributed. The graph and result of Egger’s Test (online supplemental figure S5 and table S5) also indicated no significant publication bias.

However, collectively 17 studies distributed outside the dotted line of 95% CIs, indicating these trials displayed moderate to substantial heterogeneity. In addition, most studies were distributed in the middle of y-axis, which mean that sample size of above studies was medium and conclusion was moderately reliable.

**Discussion**

In this systematic review and NMA including eight non-pharmacological interventions (2826 participants), we concluded that non-pharmacological interventions may result in a reduction or slight reduction in pain intensity compared with no treatment or placebo. Both conventional meta-analysis and NMA revealed significant efficacy of non-pharmacological treatments. This comprehensive NMA put forward the first estimate of the efficacy about the non-pharmacological treatments.

Specifically, in analysis result of ranking probability, exercise therapy displayed the highest rank probability, followed by topical heat and acupuncture, which indicated that exercise was most likely...
to be the optimal option in PD management. In the previous study, Gemma Matthewman provided reliable evidence that physical activity may reduce pain intensity. Eligible trials of exercise included in our analysis encompassed several types of modified exercise: isometric exercise, relaxation exercises, Zumba exercise and stretching exercise. Synthesis of results showed the range of 1.94–5.1 in pain reduction (generally in one or two menstrual cycles), which exceeded the clinical significance of 2 in the 0–10 scale. Among included studies, participants usually performed the exercise from the third day to the end of treatment, or within non-menstrual period. It was reported that cramp and somatic symptom behaved obviously in first 3 days of menstrual cycle.

With regard to the pathogenesis and therapeutic mechanism of PD, several researches concluded that the increased production of PGs cause uterine hypoxia and ischaemia, thus leading to abdominal cramp. On one hand, exercise motivates uterine blood flow and cyclic metabolism, relieving uterine hypoxia and ischaemia, which results in reduction of pain. Dmitrovć reported that the increased blood flow in the uterus would remove the excess level of PGs in the respective region and reduce uterine contractions. On the other hand, female with PD reported significantly lower QOL due to physical pain, psychological and emotional distress. Prevalence research showed that 14.9% of women with PD were suffering from insomnia in their menstrual bleeding period. Another study revealed significant improvement in sleep quality by the Pittsburgh Sleep Quality Index in the experimental group after exercise. Priya Kannan's research showed average variation of 4.8 in the Mental Component Summary score of the SF-12 in follow-up period (7 months).

Figure 3  Forest plot for pain intensity (VAS) in comparison of acupuncture versus no intervention.

Figure 4  Forest plot for pain intensity (VAS) in comparison of exercise versus no intervention.
We included three trials in acupuncture therapy which adopted no-treatment control, and acupuncture ranked the third in probability analysis. Two trials measured pain intensity (VAS) through the period of 3 cycles, and probably resulted in a reduction of pain intensity compared with control group (3.66 vs 1.68, 4.76 vs 0.05). Another one trial measured outcome post-treatment once time (3.46 vs 0.91 post vs pre). With regard to the mechanism of analgesic effect, acupuncture may repair the inflammatory environment of uterus through nuclear factor-κB signalling pathway. Speculation was also put forward that analgesic effect may be linked to the limbic–paralimbic–neocortical network modulation involving the thalamus.

Interestingly, some researcher associated the analgesic effect of acupuncture with the placebo effect. Within the trials investigating the efficacy of acupuncture, the trials adopted placebo control exerted better efficacy than the trials adopted blank control. Above result suggested that the analgesic effect may contribute to the placebo effect; however, the reliability need further verified. According to our analysis result, short-term analgesic effect (2–3 cycles) of acupuncture was strenuously recognised, whereas the number of qualified trials is relatively scarce.

To our surprise, pairwise analysis of acupressure showed contradictory outcome. When we respectively compared acupressure with two types of control interventions (placebo for two trials and no-treatment for four trials), and consequently the comparison of acupressure versus placebo showed better efficacy than the latter comparison. The discrepancy may be attributed to the different time point of evaluation, in which 3 hours post intervention of placebo-controlled trial. On the contrary, if researcher evaluated outcome after three menstrual cycles treatment, the analgesic effect gradually attenuated. In summary, the optimal treatment period of acupressure may be constrained within 1–3 menstrual cycles.

Lastly, node-splitting analysis was conducted to assess the consistency in network analysis, and the result indicated no significant between-trial heterogeneity in the analysis. In general, heterogeneity is influenced by several factors, such as baseline characteristic, sample size. Among 8 pairwise comparisons of non-pharmacological treatment, 6 comparisons compromising 22 trials showed relatively high heterogeneity (I²≥75%). We speculated that the heterogeneity was potentially attributed to small sample size (majority were less than 50). Ensuring the eligible sample size of trials (> 400) is conducive to decrease between-trial heterogeneity and network inconsistency.

Strengths and limitations
To our knowledge, it is the first network-analysis that comprehensively integrated the available evidence of non-pharmacological interventions used for PD management. Only RCT were included in our NMA, ensuring rigorous design and thus providing eligible quality evidence.
Nevertheless, this NMA has several limitations that should be acknowledged. First, the sample size of several included studies was small (<50), thereby the reliability of the data may be insufficient. In addition, the number of included interventions were relatively small (eg, topical heat-2 TENS-3), thus possibly restricting the strength of evidence. Second, due to the scanty of research, we were unable to conduct comparisons and network-analysis among other non-pharmacological interventions (eg, moxibustion, spinal manipulation). Third, pain intensity (VAS) was the sole measure to be evaluated in the analysis. Finally, most of the included studies were conducted in Asian countries; the lack of sample from other continents may restrict the further generalisation worldwide.

Conclusion
Non-pharmacological interventions may result in a reduction or slight reduction in pain intensity compared with no treatment or placebo. Specifically, exercise and acupuncture are considered as potentially effective non-pharmacological treatments in short-term treatment. Indeed, larger and better methodological quality research is needed.

Contributors
XL contributed to the study concept and design and drafted the manuscript. XL contributed to preparation and analysis of the data. XH took responsibility for the integrity of the data and verify the accuracy of the data analysis. J-PH and J-JL contributed to the interpretation of the data and critically reviewed the manuscript for publication. XL is designated as guarantor to accept full responsibility for the work.

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None declared.

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