INPLASY PROTOCOL

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Corresponding author:
Jian-Ping Liu

liujp@bucm.edu.cn

Author Affiliation:
Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine

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None.

The effect of navel therapy on pain relief and quality of life in patients with primary dysmenorrhea: systematic review and meta-analysis

Yan, LJ[1]; Wang, ZJ[2]; Liang, SB[3]; Fang, M[4]; Liu, JP[5].

Review question / Objective: **If navel therapy is effective on pain relief and quality of life in patients with primary dysmenorrhea, when compared with a placebo, no treatment, or usual care.**
Condition being studied: **Primary dysmenorrhea (PD), defined as painful cramping of menstrual origin in adolescents and mature women with normal pelvic anatomy, begins a few days before menstruation and persists for 48 to 72 hours. It usually comes with a wide range of physical symptoms, such as headaches. The leading physiological factor in PD is the increased amounts of prostaglandins in the menstrual fluid, especially PGF2α, which results in myometrial contractions, reducing uterine blood flow and causing uterine hypoxia, then leading to the painful cramping. PD remains an important women's health issue with incidence ranging from 41.7% to 89.1% in groups of different ages and nationalities, and has medical, social, and economic consequences.Conventional treatments have focused on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the oral contraceptive pill (OCP), both of which work as prostaglandin synthetase inhibitors, producing a direct effect on uterine smooth muscle to reduce myometrial activity. However, long-term use of NSAIDs has been associated with side effects such as headache, dizziness, drowsiness, loss of appetite, nausea, vomiting, gastrointestinal bleeding, increased acute asthma, dysuria, and acne. Other evidence-based approaches to effectively managing symptoms of dysmenorrhea are therefore needed.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 January 2021 and was last updated on 01 January 2021 (registration number INPLASY202110003).

INTRODUCTION

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Condition being studied: Primary dysmenorrhea (PD), defined as painful cramping of menstrual origin in adolescents and mature women with normal pelvic anatomy, begins a few days before menstruation and persists for 48 to 72 hours. It usually comes with a wide range of physical symptoms, such as headaches. The leading physiological factor in PD is the increased amounts of prostaglandins in the menstrual fluid, especially PGF2α, which results in myometrial contractions, reducing uterine blood flow and causing uterine hypoxia, then leading to the painful cramping.PD remains an important women's health issue with incidence ranging from 41.7% to 89.1% in groups of different ages and nationalities, and has medical, social, and economic consequences. Conventional treatments have focused on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the oral contraceptive pill (OCP), both of which work as prostaglandin synthetase inhibitors, producing a direct effect on uterine smooth muscle to reduce myometrial activity. However, long-term use of NSAIDs has been associated with side effects such as headache, dizziness, drowsiness, loss of appetite, nausea, vomiting, gastrointestinal bleeding, increased acute asthma, dysuria, and acne. Other evidence-based approaches to effectively managing symptoms of dysmenorrhea are therefore needed.

METHODS

Search strategy: We searched for a wide range of sources to find both published and unpublished studies via the following electronic databases and grey literature sources by two authors. The major Chinese electronic databases include China National Knowledge Infrastructure (CNKI) (1911–December 2020), Chinese Scientific Journal Database (VIP) (1989-December 2020), Chinese Bio Medical Literature Database (CBM) (1978–December 2020), and Wanfang Database (Wanfang) (1994–December 2020). PubMed (from inception-December 2020) and the Cochrane Library (Issue 4, 2020), Embase(from inception-December 2020), Web of Science (1900-December 2020). We searched trial registries from inception to December 2020 via ClinicalTrials. The terms used in the literature for navel therapy according to the initial search. In order to find out all the related papers, the searching terms to be used in Chinese databases include “qiliao”,”shenque”,”tieqi”,”Tianqi”,”naqi”,”tuqi”,”fuqi”,“zhengqi”, ”jiuqi”, ”moqi”, ”rouqi”, ”fengqi”, ”yanqi” , ”qijiu”, “qifu” ,”tieqi” .The searching term used in English databases is: Shenque, CV8. The terms for dysmenorrhea include "dysmenorrh*" Or (menstrua* and pain*)Or(menstrua* and distress*) Or (menstrua* and cramp*)Or "pelvic pain" .No language restrictions was applied, and translations will be sought when necessary.

Participant or population: We will include female patients suffering from primary dysmenorrhea. According to Primary Dysmenorrhea Consensus Guideline developed by Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2017, the definition of primary dysmenorrhea was based on cyclic pelvic pain during menstruation without any identifiable gynecological pathology as indicated by pelvic examination, such as endometriosis, adenomyosis, or uterine myoma.

Intervention: Navel therapy, which means applying specific stimulation to the umbilical cord to achieve the therapeutic effect. The methods of stimulation include acupuncture, moxibustion, massage, drug filling, cupping, etc, or a combined stimulation method. Studies will be considered if participants in the group received navel therapy that is used alone or combined with routine pharmacotherapy (e.g. aminosalicylate) and general adjuvant therapy or usual care.

Comparator: Types of control interventions included in our studies are no treatment, placebo treatment, and usual care such as NSAIDs and OCs. Combined therapy with navel therapy and other interventions compared with other interventions alone will be also included, navel therapy

combined with other TCM therapies (including acupuncture) compared with non-TCM therapies will be excluded.

Study designs to be included: All randomized controlled trials (RCTs) are eligible for inclusion. We include cross-over trials if they had pre-cross-over data.

Eligibility criteria: All randomized controlled trials (RCTs) are eligible for inclusion. We will include cross-over trials if they had pre-cross-over data. We will include female patients suffering from primary dysmenorrhea. Randomized studies of navel therapy, either as the sole treatment or as an adjunct to other treatments applied in both groups (intervention and control groups) in the same manner, will be included. Types of control interventions will include in our studies were no treatment, placebo treatment, and usual care such as NSAIDs and OCs. Combined therapy with Navel therapy and other interventions compared with other interventions alone will be also included, navel therapy combined with other TCM therapies (including acupuncture) compared with non-TCM therapies will be excluded.

Information sources: In terms of source of literature and search strategy, we searched for a wide range of sources to find both published and unpublished studies via the following electronic databases and grey literature sources by two authors. The major Chinese electronic databases include China National Knowledge Infrastructure (CNKI) (1911–December 2020), Chinese Scientific Journal Database (VIP) (1989-December 2020), Chinese Bio Medical Literature Database (CBM) (1978–December 2020), and Wanfang Database (Wanfang) (1994–December 2020). PubMed (from inception- December 2020) and the Cochrane Library (Issue 4, 2020), Embase(from inception- December 2020), Web of Science (1900- December 2020). We searched trial registries from inception to December 2020 via ClinicalTrials." We sought further information from the authors of relevant studies if study findings were unclear or missing.

Main outcome(s): 1.Pain intensity, as a continuous variable measured preferably by the visual analogue scale (VAS) or other validated scales. Pain relief, measured as dichotomous outcomes (i.e. pain relief: yes or no). 2.The duration of pain:the number of hours they felt the pain during te first three days of menstrual bleeding 3.Quality of life, measured by a validated scale, for example the Short Form (SF) 36.We only include trials reported pain intensity or quality of life in the result part.

Additional outcome(s): 1. Overall improvement in generic menstrual symptoms (e.g. nausea, tiredness) measured by changes in overall dysmenorrhea symptoms that were either self-reported or investigator-observed, or any other similar measures. 2. Reported use of additional medication, measured as the proportion of women requiring analgesics. 3. Restriction of daily life activities, measured as the proportion of women who reported activity restrictions. 4. Absence from work or school, measured as the proportion of women reporting absences from work or school, and also as hours and days of absence as a more selective measure. 5. Adverse effects from treatment, measured as incidence of side effects and types of side effects.

Quality assessment / Risk of bias analysis: We will assess the risk of bias in included RCTs using the Cochrane's 'Risk of bias' tool. This includes assessment of: •method used for generating the randomization sequence allocation of participants to thetreatment arms; • allocation concealment; • blinding (of participants, healthcare providers and outcome assessors); • reporting of incomplete outcome data (studies were considered at high risk of bias if more than 80% of people were assessed for primary outcomes): proportion of losses to follow-up and association with treatment arms, reasons for drop-out and association of drop-outs with treatment arms; • selective reporting of outcomes; • any other sources of bias that were pre-defined as carry-over effects and unbiased data available for analysis for cross-over trials We assessed publication

bias by using a funnel plot if 10 or more studies were included.

Strategy of data synthesis: Statistical analyses were performed with the program Review Manager (ver. 5.3 Copenhagen: Te Nordic Cochrane Centre, Te Cochrane Collaboration, 2014). Trials were combined according to the type of intervention and type of outcome measure and/or control. Data will be pooled and expressed as the mean diference (MD) or standardized mean diference (SMD) for continuous outcomes, as RR for dichotomous outcomes.

Subgroup analysis: When substantial heterogeneity was detected, we explored the sources of heterogeneity by performing a subgroup analysis according to the type of intervention (e.g. cupping on Shenque, moxibustion on Shenque, herb medcine patching on Shenque, et al) ,control group or syndrome types of TCM. If some factors (e.g., lack of included trials, large methodological or clinical diferences among trials) were found, we did not conduct a subgroup analysis or data synthesis, but instead created a narrative description of the included studies. We assessed publication bias by using a funnel plot if 10 or more studies were included.

Sensibility analysis: Furthermore if necessary, a sensitivity analysis will be performed.

Country(ies) involved: China.

Keywords: Navel therapy, Shenque, Traditional Chinese Medicine, Clinical studies, Systematic review

Contributions of each author:
Author 1 - Li-jiao Yan.
Author 2 - Zhi-jie Wang.
Author 3 - Shi-bing Liang.
Author 4 - Min Fang.
Author 5 - Jian-Ping Liu.