Herbal medicine (Danggui-Shaoyao-San) and Ear Acupoint Pressing Beans in the treatment of dysmenorrhea caused by endometriosis and adenomyosis: a study protocol randomized controlled trial

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Abstract

Endometriosis and adenomyosis are two of the most common causes of secondary dysmenorrhea and often lead to a deterioration in the quality of life. Traditional Chinese medicine and acupuncture are widely used in the treatment of menstrual pain in clinical practice. Danggui Shaoyao San (DSS) and ear acupoint pressing beans may constitute an effective treatment strategy for women with dysmenorrhea due to endometriosis and/or adenomyosis, although evidence is limited.

Methods/design This randomized, controlled clinical trial aims to recruit patients who suffer from menstrual pain due to endometriosis and/or adenomyosis to evaluate the efficacy and safety of DSS and auriculotherapy. Primary outcome measures are Visual Analog Scale (VAS), Short-Form McGill Pain Questionnaire (SF-MPQ), dysmenorrhea symptoms and traditional Chinese medicine correlative time points.

Discussion This pivotal trial will be a standardized, scientific, clinical trial designed to evaluate the use of DSS and auriculotherapy in the treatment of dysmenorrhea due to endometriosis and/or adenomyosis. The trial will also conform to the international standards of clinical trials for the recognition of traditional Chinese medicine. Trail registration Chinese Clinical Trail Registry, ID: ChiCTR-IOR-17013829

Registered on 11th December 2017 Keywords: Danggui Shaoyao San; Ear pressing beans; Endometriosis; Adenomyosis; Dysmenorrhea; Randomized controlled trial

1 Background

Endometriosis and adenomyosis are two of the most common causes of secondary dysmenorrhea. Endometriosis is found in 70%-90% of patients complaining of pelvic pain (1-3) while adenomyosis is considered to be a subtype of endometriosis that is confined to the uterine wall. Both conditions may cause dysmenorrhea and infertility. First-line treatment options for pain due to endometriosis include nonsteroidal anti-
inflammatory drugs (NSAIDs), oral contraceptives (OC) and progestogens (4). Hormone therapy, such as gonadotropin-releasing hormone agonist (GnRHa) and the levonorgestrel-releasing intrauterine system (LNS-IUS), is widely used in the treatment of adenomyosis and endometriosis (5,6). However, the high recurrence rate, side effects and severe adverse events associated with these treatments lead patients to seek supportive complementary and alternative forms of medicine (CAM) (7). Examples of such CAM therapies for dysmenorrhea include acupuncture-related therapies (8-11), as well as Chinese herbal medicine (CHM) (12-18). Danggui-Shaoyao-San (DSS), also known as Toki-Shakuyaku-San or TJ-23, is a widely used traditional formulation of Chinese medicine (TCM) derived from “Jin Kui Yao Lue”, first described by Zhong-Jing Zhang in the Eastern Han Dynasty. DSS consists of six Chinese herbs: Radix Paeoniae Alba, Radix Angelica sinensis, Rhizoma Chuanxiong, Poria cocos, Rhizoma Atractylodis macrocephalae, and Rhizoma Alismatis. For thousands of years, DSS has been used as a blood-activating and stasis-eliminating drug to treat gynecological disorders, including dysmenorrhea, amenorrhea and infertility (19,20). DSS is believed to mediate ovarian hormones (21), estrogenic activity (22) and neurotoxicity (23). Auriculotherapy, or auricular point therapy (APT), has been found to relieve menstrual pain in patients with dysmenorrhea and endometriosis (24-27). However, the application of this treatment modality currently doesn’t meet the Good Clinical Practice standards. In order to assess and add the proper application of TCM and Ear Acupoint Pressing Beans, precise studies are now needed to confirm the safe and effective use of Chinese herbal medicines and APT for the treatment of dysmenorrhea caused by endometriosis and adenomyosis.

Here, we describe a protocol for a randomized, controlled clinical trial to evaluate the safety and effectiveness of the use of DSS and APT in the treatment of gynecology conditions.
2 Methods/design

2.1 Study design

This study is a randomized, controlled, clinical pilot trial. We will select patients who experienced dysmenorrhea caused by endometriosis and adenomyosis between November 2017 and December 2019 at Guangdong Provincial Hospital of Chinese Medicine. Patients will be randomly assigned to the following groups: (1) Danggui Shaoyao San (DSS) group; (2) Danggui Shaoyao San (DSS) and auricular point therapy (APT) group and (3) oral contraceptives (OC) group. This will be carried out according to stratified random sampling and each patient will be allocated a random number (corresponding to numbered drugs). We will then evaluate the efficacy and safety of Danggui Shaoyao San (DSS), and ear acupoint pressing beans, for patients by comparing a range of indices between different groups, including the relief of pain, serum CA 125 level, hepatorenal function, coagulation function and electrocardiograms. The study protocol will be certified by the Institutional Review Board (IRB) of The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine), and registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/, ChiCTR-IOR-17013829). The below inclusion criteria, exclusion criteria, and elimination criteria will be followed to ensure the accuracy of results.

2.2 Inclusion criteria

1) Patients with dysmenorrhea caused by endometriosis or/and adenomyosis

2) Traditional chinese medicine syndrome, blood deficiency and blood stasis

3) Aged 18-42 years, Non-menopausal females with a regular menstrual cycle (23-37 days)

4) Provision of signed and informed consent

2.3 Exclusion criteria

1) Surgical treatment of patients in the near future
2) Patients with other severe gynecological conditions, including pelvic infection and
gynecological malignant tumor(s)
3) Cardiovascular, liver, kidney, brain, lung co-morbidity, or other serious disease
4) Metal disability
5) Serum CA 125 \(\leq 200\) U/ml
6) Ovarian endometrioma maximum anteroposterior diameter \(\leq 5\) cm, or other ovarian
cystic-solid/solid mass maximum anteroposterior diameter \(\leq 5\) cm
7) Uterine leiomyomas with a maximum steroposterior diameter \(\leq 5\) cm
8) Use of hormones, or other medications, including GnRH-a, during the past 3 months
9) Secondary dysmenorrhea cause by other diseases, except for endometriosis and
denomyosis
10) Patients who plan to become pregnant in 6 months.

2.4 Study withdrawal and stopping medication
1) Serious complications, or requiring other treatments during the study
2) Other complications arising due to interventions, including severe allergy or serious
adverse events
3) A worsening condition that cannot be controlled
4) Refusal to continue the treatment, regardless of the reason

This part mainly depend on LXC, XFL and other experienced gynecology professor.

2.5 Trial procedure
The entire trial includes 3-menstrual cycle intervention phases and a 3-menstrual cycle
follow-up phase. Participants will be randomized to receive one of three treatments (DSS,
DSS in combination with APT (DSS+APT), or OC therapy) through a stratified
randomization system, and acquire a random number (corresponding to the DSS group,
DSS+APT group and OC group). Subjects in the DSS and DSS+APT groups will be
instructed to apply the DSS decoction twice every day, beginning two weeks prior to the menstrual period for 21 days. Subjects in the DSS+APT group will undergo APT twice a week during the three weeks they take DSS. Subjects in the OC group will take one tablet daily, beginning on day five of their menstrual cycle, and continuing for 21 days. Subjects will be evaluated once a month and results recorded in a Case Report Form (CRF) until the study is completed. A participant flowchart is shown in Fig. 1 and the Standard Protocol Items will be as follows. A ‘Recommendations for Interventional Trials (SPIRIT)’ Figure for the trial is shown in Table 1. Adverse events will be monitored during face-to-face and telephone interviews throughout the study. For participants, during this six-month, related medicine or treatment are banned.

2.6 Interventions

The oral DSS decoction used in the study will be produced by the TCM pharmacy of Guangdong Provincial Hospital of Chinese Medicine, which holds a Good Manufacturing Practice certificate. Both DSS and DSS+APT group subjects will be provided with individually packaged doses of DSS decoction, with instructions stating that each dose should be heated in warm water and consumed twice daily, beginning two weeks prior to menstruation, for a total duration of three weeks.

All acupuncturists with TCM certification will receive specific practical training prior to the study. APT group subjects will undergo APT twice a week, beginning two weeks prior to menstruation and lasting a total of three weeks. The set of auricular points will include Ear-Shenmen (MA-TF1), Sympathetic (AH6a), Uterus (TF2), Subcortex (AT4), and Kidney (MA-SC). One auricle will be sterilized with 75% alcohol and the supra-auricular points will be treated with Wang Bu Liu Xing (cowherb seeds) in desensitized plasters (5×5 mm). Ears will be alternated every three days.

Subjects in the OC group will take one tablet daily, starting on day five of their menstrual
cycle, and continuing for 21 days.

2.7 Randomization

The study leader (LXC and LXF) will create random sequences using envelopes. Randomization will take place as soon as subject eligibility requirements are met. Participants will be randomized into one of the three treatment groups (DSS, DSS+APT, or OC). Random numbers will be generated by using a special website, http://www.gztcmgcp.com/sjxt/login.asp and saved by statistical professionals.

2.8 Quality control

To ensure that this research will be good quality, this study protocol has undergone repeatedly amendment and alteration by gynecological disease specialists, skilled acupuncturists, professional statisticians and experienced methodologists. The entire study routine will be operated by independent qualified inspectors. The CRF will be filled out under the guidance of the CRF instructions. Original medical history and data recorded in the CRF, will not be modified afterwards. Any record alteration must be mark in detail and accompanied by a signature of the individual making any changes. All laboratory and clinical data is to be recorded rigorously, and all significantly abnormal data will be reappraise. Physicians will be required to make any necessary notes in response to such information.

2.9 Outcome measures

Our primary outcome measures are as follows: Visual Analog Scale (VAS) for pain, Short-Form McGill Pain Questionnaire (SF-MPQ), Dysmenorrhea symptom timepoints and TCM correlative symptom timepoints.

Our secondary outcome measures include pelvic examination, serum CA125, T lymphocyte subset levels, B lymphocyte subset levels, natural killer (NK) cell levels in human peripheral blood mononuclear cells (PBMCs), transvaginal/transrectal ultrasound (volume
of the uterus and ovary, maximum anteroposterior diameter of the ovarian endometrioma).

2.10 Safety assessments
Routine blood tests, liver and kidney function tests, and an electrocardiogram will be performed both before and after treatment. Any adverse events will be observed and recorded in detail at any time during the treatment phase, as well as the follow-up phase. Measures will be taken in time when adverse events happens.

2.11 Estimation of sample size
Our sample size estimation is based upon previous prospective clinical studies (28). The efficacy of DSS is assumed to be 95%. However, due to the lack of existing data relating to the efficacy of APT, we cannot rely upon the literature for sample size determination.

Instead, we hypothesized that the order of efficacy for the treatments will be as follows: DSS+APT[DSS = OC. PEMS 3.1 (Package for Encyclopaedia of Medical Statistics, Si chuan, China) software for Windows was used to randomly assign patients to one of three treatment groups. The rounded sample size for each group was 54. Assuming a 10% dropout rate, the final sample size would be 60 for each group. Therefore, 180 participants will be recruited. Guangdong Provincial Hospital of Chinese Medicine, which owns large number of outpatients, and experienced project directors ensure the trials progress.

2.12 Data collection and statistical analyses
Data will be collected and recorded in CRF forms via doctors’ office visiting and telephone follow-ups; this will occur once every menstrual period. The Epidata 3.1 Statistical Package will be used for data input. Two people will perform data entry independently; these people will be trained before and tested prior to starting work. The data will then be analyzed using the Statistical Package for the Social Sciences (SPSS) software (IBM,
Armonk, NY, USA.)

The data will be analyzed by an independent statistician. For measurement data, the mean, standard deviation (SD), minimum value, maximum value, and median will be used for comparison.

Differences among groups in categorical data will be analyzed by analysis of variance (ANOVA) and pair-wise comparison, while heteroscedasticity data or abnormal distribution will be analyzed by the rank-sum test and pair-wise comparison. If the data are divided as count data, the constituent ratio and frequency will be appropriate for comparison. The chi-square test at an \( \alpha = 0.05 \) given a 2-sided test will be suitable for analysing efficient intergroup difference.

3. Discussion

Endometriosis and adenomyosis are estrogen-dependent conditions, which result in dysmenorrhea (i.e., menstrual and chronic pain), which occurs in young to middle-aged adult women. A variety of treatments are used by clinicians to reduce such pain, including surgery, NSAID, OC, progestogen, danazol, GnRH-a, and anti-progestogen medications (29). Acupuncture is an adjunctive therapy for pelvic pain associated with endometriosis. Two randomized studies have previously evaluated specific versus sham acupuncture for endometriosis pain and both reported significantly better pain relief with true acupuncture (30,31). In addition, previous randomized clinical trials, comparing Chinese herbal medicine treatment to gestrinone and danazol, concluded that Chinese herbal medicine had comparable results, but with fewer side effects (32). Taking into consideration the TCM “same treatment for different diseases and different treatments for the same disease” therapeutic principle, we designed this study to evaluate the efficacy and safety of Chinese herbal medicine DSS and APT for the treatment of menstrual pain due to endometriosis and/or adenomyosis, and to provide a scientific basis/rationale for the
clinical application of these two treatments.

This study was designed to evaluate the efficacy and safety of Danggui Shaoyao San (DSS), and ear acupoint pressing beans, for the treatment of dysmenorrhea associated with endometriosis and adenomyosis. We also wished to provide a scientific basis for therapy efficacy.

List Of Abbreviations:

APT: Auricular points therapy
CAM: Complementary and alternative medicine
CHM: Chinese herbal medicine
CONSORT: Consolidated Standards of Reporting Trials
CRF: Case Report Form
DSS: Danggui Shaoyao San
GCP: Good Clinical Practice
ITT: Intention-to-treat
LOCF: Last observation carried forward
NSAIDs: Nonsteroidal anti-inflammatory drug
OC: Oral contraceptives
SF-MPQ: Short-Form McGill Pain Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPSS: Statistical Package for the Social Science
TCM: Traditional Chinese Medicine
VAS: Visual Analog Scale for pain

Declarations:

Ethics approval and consent to participate
The IRB of Guangdong Provincial Hospital of Traditional Chinese Medicine approved the study protocol. (Ethical reference: B2017-158-01. Verbal informed consent will be obtained from all study participants.)

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Trial status: Participants are currently being recruited.

The date recruitment began at November 2017; the approximate date when recruitment will be completed: December 2019.

Hospital: Guangdong Provincial Hospital of Chinese Medicine.

Protocol version number: TRLS-D-19-00331 (Version number: 3.0)

Author contributions

XFL and LXC developed the study protocol. YZT and JYW coordinate the study. WJY and YXH is responsible for enrolment and data collection. WJY drafted the manuscript in collaboration with YZT. All authors have read and approved the final version of the manuscript.
manuscript.

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**Trail registration**

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Table

Due to technical limitations the table could not be inserted here. It an be found as an image file in the supplemental files.

Figures

![Study Flowchart](image)

**Figure 1**

Study Flowchart.

**Supplementary Files**

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Table 1.tiff
Information Leaflet for Informed Consent 20190410.doc
SPIRIT-Checklist-for randomised studies 20190410.doc