External Chinese medical therapy for pain associated with hyperplastic disease of the breast: study protocol of a randomized, double-blind, multicenter, controlled trial

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BACKGROUND: Hyperplastic disease of the breast (HDB) is caused by a hormone imbalance experienced among women at a certain age. Slight breast pain is common in women before menstruation without need of treatment; however, if the pain becomes severe, it can cause physical and mental suffering. Therefore, it is of great clinical significance to control this disease.

METHODS AND DESIGN: This study will follow the principle of evidence-based medicine and adopt various design methods, being conducted as a randomized, controlled, double-blind and multicenter trial based on the cause of HDB defined in Chinese and Western medicine. According to the cause of HDB in Chinese and Western medicine and its pathogenesis and prognosis, this study will conduct syndrome differentiation, adopt external therapy of Chinese medicine by using Sanjie Zhitong plaster as the intervention, take placebo as the control method and aim at relieving pain. The effectiveness and safety of Chinese medicine therapy will be evaluated. During the design process, some confounding factors will be taken into consideration and prevented with corresponding measures. We will also discuss the side effects of the medicine used and corresponding countermeasures to be taken.

DISCUSSION: On the basis of traditional Chinese medicine (TCM) theory, Sanjie Zhitong plaster takes the advantage of external therapy of TCM. According to the main etiology and pathogenesis of HDB, the treatment principles of warming the meridians and activating blood, smoothing circulation and relieving pain, and removing swelling and dissipating stagnation are put forward. The medicine exerts its effects directly on the lesion site by permeating into the skin and stimulating the meridians, thus improving blood supply to the breast and relieving pain.

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KEYWORDS: external therapies; fibrocystic breast disease; randomized controlled trial; clinical protocols
Hyperplastic disease of the breast (HDB) is caused by hormone imbalance when women are at a certain age[1]. Potentially the increase of estrogen or the decline of corpus luteal function causes the breast’s overreaction[2]. For histopathology, there is neither obvious fibrosis nor a clear cystic mass for the breast; gland hyperplasia can be found under the microscope; especially in the small pipe, small cyst can be formed and causes pipe expansion; the proliferation of epithelial cells of the pipe prompts the generation of nipple-like nodules in cyst or the gland hardening[3]. At certain stages, reproductive women’s breasts can change, which often manifests as breast ache, and secondly developing nodules in the breast[4]. Patients often see a doctor as the symptom of breast ache can affect their daily life and work[5].

Slight breast ache may occur to many women before their menstruation and it does not necessarily require treatment[6], but if the ache becomes aggravated and develops into a severe ache, it can bring about suffering to patients. An investigation on working women from Cardiff Hospital of England found that slight ache accounts for 45%, while serious ache 21% and half of the women had to see a doctor due to breast ache[7]. According to the studies from the previous study team, the total effective rate of herbal application to HDB can reach 70%, and the relief rate of medicine for the symptom of achiness is higher than that of medicine for nodules[8]. Integrating the previous studies with the current issue of breast ache, we will take the relief of achiness as the main target of this study; the relief of nodules and changes in estrogen levels will be taken as the secondary goal, and we will include the patients who are diagnosed as HDB and suffering from breast ache as the study subjects[9].

On the principle of Chinese medicine theory, adopting randomized, double-blind and controlled clinical trial design, this multicenter study will estimate the clinical effectiveness and safety of herbal application to HDB (attributed to a disturbance between thoroughfare vessel and conception vessel) characterized as periodic breast ache before menstruation.

1 Methods and design

1.1 Participants

1.1.1 Diagnostic criteria (1) Primary symptoms: breast pain in one breast or both breasts are swollen with menstrual or emotional changes; (2) Secondary symptoms: lumbar and knee soreness and limp, dizziness, ringing in the ears, mental and physical fatigue, chest and abdominal distension, insomnia and dream-disturbed sleep.

Primary symptoms are all necessary, and at the same time there are more than two secondary symptoms[2].

1.1.2 Inclusion criteria (1) Premenopausal females aged between 18 and 50 years old; (2) consistent with the diagnostic criteria of HDB; (3) those whose menstrual cycle is stable (28 ± 3 d) and who meet the syndrome differentiation standard of Chinese medicine for disturbance between thoroughfare vessel and conception vessel; (4) those who have suffered periodic breast ache before menstruation and the disease course lasts for a minimum of three months; (5) the moderate or severe breast ache lasting for 3 d or more than 3 d accumulatively with Visual Analog Scale (VAS) estimation ≥ 40 mm; (6) not taking Chinese or Western medicine for treating HDB and relieving breast ache in recent three months and not taking any hormone formulation, oral contraceptive or other therapeutic drugs substituted with hormones; (7) with clinical examination of breasts, at least one nodule can be palpated; (8) breast skin is smooth with no damage, ulceration or skin disease; (9) participants voluntarily accept the treatment and sign the informed consent document.

1.1.3 Exclusion criteria (1) Consistent with the diagnostic criteria of HDB but do not have periodic breast ache syndrome; (2) HDB patients...
that do not have the syndrome of disturbance between thoroughfare vessel and conception vessel; (3) metrorrhagia,  menorrhagia for more than 7 d, menopause, or with an unstable menstrual cycle; (4) patients that are diagnosed as breast neoplasm, mastitis or have other operative indications; (5) patients who have severe diseases of the cardio-cerebrovascular system, liver, kidney or hematopoietic system, gastrointestinal ulcers, severe diseases (such as tumor or AIDS), or patients with mental instability; (6) patients with abnormal laboratory indexes; (7) patients that have had breast anaplasia; (8) patients that have had their ovaries removed (whole or partially); (9) ache in front of or beside the breast caused by other diseases; (10) females that are in pregnancy or lactation period, or females that plan to be pregnant in recent three months; (11) patients of an allergic constitution, or those who are known to be allergic to the components of the formulation; (12) according to the judgment of the researchers, there may be other diseases that can reduce possibilities of entering the group, for instance, the working environment can reduce the likelihood of follow up; (13) patients who have participated in other recent clinical trials.

1.1.4 Entry procedure Outpatients from five grade III hospitals including Shanghai Longhua Hospital, Zhejiang Province Hospital of Traditional Chinese Medicine (TCM), Shanghai Hospital of TCM, Shanghai Huashan Hospital and Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. All the included patients will sign the informed consent.

1.2 Study design
1.2.1 Sample size estimation According to the formula calculation for sample size estimation of superiority-inferiority clinical trial, the effective rate of placebo applied to HDB is approximately 20% to 22%[10]; it is theorized that the effective rate of the external therapy of herbal application to HDB will be 40%. Taking ache relief or nodule reduction as the two main indexes for evaluating clinical effect, supposing that any one of the indexes is effective, then the parameter is established as \( \alpha = 0.025 \), test power 0.9, thus \( \beta = 1 - 0.9 = 0.1 \). There will be two groups in total, in proportion of 1 : 1 for each group, then sample size of each group is estimated as 139 (\( \mu_1 = 1.96, \mu_2 = 1.28, P_0 = 22\% \), \( P_1 = 40\% \), \( P = (P_1 + P_0) / 2 	imes 100\% \), \( N = (\mu_1 + \mu_2)^2 / 2P \times (1 - P) / ((P_1 - P_0)^2 = 138.6072 \approx 139) \). The loss of follow-up rate is controlled as less than 15%, then samples needed for each group is 160, and totally 320 cases will be needed for two groups.

1.2.2 Randomization method We will adopt envelope randomization method, which is in the charge of the Data Management Center in the Affiliated Hospital of Nanjing University of TCM. Participants meeting the entry criteria will be allocated into the intervention group and the control group by the envelop randomization method. By virtue of PROC PLAN (The PLAN procedure constructs experimental designs and generates randomized plans for crossed and nested experiments) process sentence from SAS statistic software, the seed number and section box are given. Random arrangement accepted by the 350 cases (intervention group and control group) is generated, that is, the therapy distribution (that is the random code list) corresponding to the serial numbers of 001-350 is listed. Each center appoints specific personnel to distribute the medicine.

1.2.3 Double blinding Double-blinding method will be adopted. The appraiser will conduct evaluation with blinding method, that is, the clinical researcher is separated from the clinical appraiser. The random code list is established by a statistician, maintained by Shanghai Longhua Hospital once sealed. The statistician packs the medicine separately. Three types of envelopes are prepared: blind-disclosure envelop for statistical analysis (only for groups with random numbers), final blind-disclosure envelop and the urgent blind-breaking envelop. The urgent blind-breaking envelop is designed to prepare an emergency letter for each case, with patient’s medicine code marked on the envelop; the sealed letter sheet indicates the group to which the patient is assigned, for the sake of urgent blinding disclosure. Each emergency letter is sent to each center along with medicine with corresponding code and is saved by the researchers. The urgent blinding disclosure can not be disclosed without suitable reason.

1.3 Interventions The experimental group is given Sanjie Zhitong plaster for external application, while the control group adopts the similar placebo application with the same appearance and smell. The consistency of appearance, color and smell for Sanjie Zhitong plaster and its placebo (both supplied by Hejingon Pharmaceutical Factory, White Cloud Mountain Pharmaceutical Factory Co., LTD, Guangzhou) is confirmed as unidentifiable by appraisers. One course of treatment will last for one menstrual cycle.

1.4 Adverse events Drug allergy may occur in clinical experimentation. If serious drug allergy occurs, the experiment will be stopped.

1.5 Outcome measures Short-form of McGill Pain Questionnaire (SF-MPQ) including the feeling score for pain rating index (PRI), sentiment score for PRI, total score of PRI, VAS and current pain intensity for PRI will be used to evaluate the pain feeling of the patients. Other measures such as B ultrasonic scanning of breasts, main physical sign according to the Chinese medicine criteria, estrogen level of blood serum will be taken.

1.6 Follow-up visit After observation, all patients will be followed up for three months to appraise pain relief and recurrence. The patients will use a VAS visual simulation report given by the researcher
for one menstrual cycle to record the most painful moment in a day and the patients need to return the VAS visual simulation report to the hospital after one menstrual cycle. The patients will get the next VAS visual simulation report after receiving questionnaire for SF-MPQ report from the researcher. The process of the second menstrual cycle is the same as the first one. If the patient suffers endurable pain within three months of follow-up, she will not need to take pills and keep recording the VAS visual simulation report. If the patient suffers unbearable pain and hopes to get medical therapy, then she will return to the hospital and the researcher will make integration appraisal before and after VAS visual simulation report. If the VAS appraisal is $\leq 40$ mm after treatment, it will be suggested to continue taking external application of Sanjie Zhitong plaster. If the VAS appraisal $\geq 40$ mm, the patient’s grouping will be analyzed. If the patient belongs to the intervention group, the external application is useless and the patient can take Ruzengning (Shenzhen Sanshun Pharmaceutical CO., Ltd, National Drug Approval Number (1999) Z-63), three pills once, three times per day but not during the menstrual cycle. If the patient belongs to the placebo group, it will be suggested to take external therapy of Sanjie Zhitong plaster. All medicine names, doses, and starting and lasting time will be recorded if medicinal intervention is involved during the following observation.

1.7 Study supervision and quality control In accordance with the requirements of the Ministry of Science and Technology of the People’s Republic of China, this study has been entrusted to the National Chinese Medicine Clinical Research Base (Data Management Center of the Affiliated Hospital of Nanjing University of TCM).

1.8 Statistical analysis Data analysis will be conducted with SPSS 12.0 software. Measurement data will be presented as mean $\pm$ standard deviation. Paired $t$-test will be used to compare the difference of before and after treatment within a group. Student $t$-test will be used for comparison between the two groups. The $\chi^2$ test and non-parameter test will be applied for changes after treatment. Statistical tests will use bilateral threshold value, with significance level $\alpha = 0.05$. Before statistical processing, data will be examined for normal distribution and corresponding correction method will be used for abnormal distributed data. See Figure 1 for the flow diagram of this clinical study.

![Flow diagram of this clinical trial](image)

**Figure 1** Flow diagram of this clinical trial
2 Discussion

There are no ideal treatment methods and drugs for HDB at present. Modern medicine asserts that this disease is caused by endocrine dysfunction and estrogen and progesterone hormone imbalance, while TCM regards that it is caused by stagnation of liver qi and kidney deficiency. At present, TCM external therapy and surgical treatment are widely used domestically, while hormone preparation and vitamin preparation are often used abroad.

Based on current achievements and existing problems of latest domestic and overseas research, this study will include patients of HDB based on a randomized, double-blind, multicenter, controlled clinical trial design. Chinese herbal application is selected as the external therapy to appraise the clinical effectiveness and security of TCM application in treating HDB and to establish therapeutic effectiveness appraisal method to improve the quality control method of clinical research of Chinese medicine external therapy. With the scientific design, strict management and reliable results, this study will provide a comprehensive therapy protocol for HDB characterized by external therapy. Meanwhile, the implementation of this trial will enhance the construction of clinical research base for Chinese medicine and supply technological support for launching relevant studies.

3 Funding

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4 Competing interests

The authors declare that they have no competing interests.

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“中药敷贴治疗乳腺增生疼痛的随机、双盲、安慰剂对照多中心临床试验”的研究方案

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背景：乳腺增生疼痛不是真正的乳房疾病，而是女性达到一定年龄，因激素失调所致。许多女性在经前期可以出现轻度的乳腺痛，并不需要治疗，如果疼痛的程度和发作次数均增加，发展到中至重度的疼痛，则会给患者带来痛苦。因此，积极有效地防治该病具有重要的临床意义。

方法与设计：本研究根据循证医学原则，采用随机、对照、双盲、多中心试验的设计方法，根据乳腺增生中、西医病因以及发病机制、预后转归等特点，进行辨识，采用中医外治法敷贴治疗，以安慰剂为对照，以缓解疼痛为主要目的。评价中医药治疗的有效性、安全性。在设计时考虑到试验过程中可能出现的偏差因素，并采用相应措施加以防范。试验过程中可能出现的一些不良反应将采取相应应对措施。

讨论：敷贴治疗乳腺增生疼痛是以中医药理论为指导，在保留传统用药的基础上，发挥中医外治法的优势。本研究根据乳腺增生的主要病因病机和乳房疼痛、肿胀、结块的临床特点，结合长期临床实践经验，提出湿经活血、理气止痛、散结消肿的治疗原则，使药物直接作用于病变部位，通过皮肤渗透吸收和对经络穴位的刺激作用，改善乳房血运，以止痛为主，散结为辅，减轻症状，并反射性调节内分泌功能。

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关键词：外治法；乳腺纤维囊性病；随机对照试验；临床方案