Effects of Chinese herbal medicine Pugongying for reducing the application of antibiotics in breastfeeding women with acute mastitis: study protocol of a randomized, active-controlled, outcome assessor-blinded trial

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Research Article

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Title

Effects of Chinese herbal medicine Pugongying for reducing the application of antibiotics in breastfeeding women with acute mastitis: study protocol of a randomized, active-controlled, outcome assessor-blinded trial.

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Abstract

- **Background**: Acute mastitis influences the health condition and quality of life of the infants and mothers during the lactation. Pugongying (a kind of Chinese patent medicine, *Herba Taraxaci*) has shown benefits in lactating women with acute mastitis in clinical practice. However, there is no solid evidence to support its effectiveness and safety.
- **Methods**: A three-arm, multicenter, randomized, active-controlled, outcome assessor-blinded clinical trial will be undergoing in three hospitals in Beijing. 306 participants will be randomly assigned into three groups in 1:1:1 ratio with Pugongying alone, cefdinir alone, and combination of Pugongying and cefdinir for 3-day intervention drugs administration. And in combination of Pugongying and cefdinir group, the participants will be administrated with 2-day cefdinir and 3-day Pugongying. The primary outcomes are resolution of fever, visual analogue scale (VAS) scores of breast pain, and the size of the breast mass by palpation. The secondary outcomes are the patency of milk, Traditional Chinese Medicine (TCM) symptoms scores, white blood cell count, the percentage of neutrophil and C-reactive protein, relapse at 3th day of follow up after completion of treatment, and safety assessment including routine blood, liver and renal function and electrocardiography. Besides, the incidence of surgery and the quantity of additional intervention drugs will also be evaluated.
- **Discussion**: The results of this trial are expected to confirm whether Chinese herbal medicine Pugongying could alleviate the symptoms and signs in lactating women with acute mastitis, and they could reduce application of cefdinir in clinical practice.
- **Trial registration**: ClinicalTrials.gov [Home - ClinicalTrials.gov], ID: NCT03756324. Registered on December 18th 2018.

https://www.clinicaltrials.gov/ct2/show/NCT03756324?cond=Acute+mastitis&draw=2&rank=1

Keywords

Cefdinir, *Herba Taraxaci*, Mastitis, Pugongying granule, Traditional Chinese medicine.

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Effects of Chinese herbal medicine Pugongying for reducing the application of antibiotics in breastfeeding women with acute mastitis: study protocol of a randomized, active-controlled, outcome assessor-blinded trial
Trial registration {2a and 2b}.	ClinicalTrials.gov, ID: NCT03756324. Registered on December 18th 2018, https://www.clinicaltrials.gov/ct2/show/NCT03756324?cond=Acute+mastitis&draw=2&rank=1 Item 2b: Not applicable, as the study is not registered on World Health Organization Trial Registration Data Set.
Protocol version {3}	Version 1.0. Date: May, 2018.
Funding {4}	This trial is supported financially by the 2018 Capital's Funds for Health Improvement and Research (CFH 2018-7032).
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Name and contact information for the trial sponsor {5b}	Investigator initiated clinical trial: Xiao-hua Pei (Principal Investigator) pxh_127@163.com.
Role of sponsor {5c}	This is an investigator initiated clinical trial. Therefore, the sponsor is not involved in study design, collection, analysis and interpretation of data, writing of the report and submission of the manuscript for publication.

Introduction

Background and rationale {6a}

Acute mastitis is a common problem in lactating women.[1] It is defined that part of one breast becomes red, painful, swollen and hard, sometimes with common symptoms of fever and malaise.[1] The prevalence rates of acute mastitis in breastfeeding women range from 2% to 33% according to previous mastitis prevalence data.[1] Acute mastitis may produce overwhelming acute symptoms that causes women to consider to stop

breastfeeding, or health-care workers will advise women who are administered antibiotics therapy to stop breastfeeding, both of which will result in breastfeeding failure and the infants lose their optimal nutrition.[1-2] What's more, acute mastitis also can bring severe complications such as breast abscess, and occasionally be fatal if inadequately treated.[1] These conditions can lead to a considerable burden of disease and involve substantial costs.[3] Previous studies have indicated that Gram-positive staphylococci is the main pathogenic bacteria in acute mastitis.[4-7] With the increasing application of metagenomic sequencing technology in milk microecology field, the research methods of acute mastitis pathogenic bacteria have gradually turned from the isolation and cultivation of pathogens to equilibrium between microorganism. And these studies suggest that two theories may explain the occurrence of acute mastitis. One is that *Staphylococcus* and *Corynebacterium* could not be inhibited by commensal bacteria, the other is lower microbial diversity in milk, with increased abundance of conditioned pathogens and depletion of commensal obligate anaerobes.[8-10] The pathogenesis of acute mastitis has not been thoroughly described, but most investigators prefer that dysbiosis of milk microbiome and/or bacterial infections contribute to the condition. Non-pharmacological measures that have shown promise include effective milk removal, rest, adequate fluids and nutrition, and cold packs application to the breast.[2] Pharmacological measures that have been recommended include analgesia (ibuprofen) and antibiotics.[2, 11] The role of probiotic in prevention and treatment is under determined.[2] The preferred antibiotics are usually penicillinase-resistant penicillins, such as dicloxacillin or flucloxacillin, or as recommended by local antibiotic sensitivities.[2] In China, cephalosporin is widely used in clinical practice. However, mistaking antibiotic can affect the physical function, even infants breastfeed in clinical observation.

Chinese herbal medicine is one of the most common traditional interventions in China.[12] Acute mastitis belongs to the syndrome of heat stagnation in both liver and stomach in Traditional Chinese Medicine (TCM) theory. The stomach receives food and drink, and the liver governs free flow of qi. The stagnation qi of stomach is due to dietary irregularities, and the stagnation of liver is due to the failure of liver to disperse qi resulted from emotional depression, which can both result in qi depression transforming into fire. In TCM rationale, breasts belong to stomach meridian and nipples belong to liver meridian.[13] Thus, lactating women with acute mastitis manifest part of usually one breast becoming red, painful, swollen and hard.

Pugongying herbs (*Herba Taraxac*i) can alleviate the syndromes of acute mastitis. Pugongying Granule (Pugongying) is a kind of Chinese patent medicine and its indications include acute mastitis. It has been

approved by China Food and Drug Administration (CFDA) in 2015. The main ingredient of Pugongying Granule is Pugongying herbs. The action of Pugongying is to clear liver and stomach heat. Some pharmacological studies have showed that Pugongying has a broad spectrum of antimicrobial activity, and can balance microorganism.[14-17] At the same time, Pugongying can also promote the production of milk and maintain the patency of milk well. [18] The previous clinical trial (unpublished) that had been conducted in the Third affiliated hospital of Beijing University of Chinese Medicine, has demonstrated that Chinese herbal medicine can act better than cefdinir in the time to resolution of fever and visual analogue scale (VAS) scores of breast pain. Although Pugongying has demonstrated positive effects on acute mastitis in clinical practice, rigid validation using a randomized controlled trial remains the best way to examine the effects of Pugongying in lactating women with acute mastitis.

Objectives {7}

We hypothesize that Pugongying have positive effects on fever-resolution, less breast pain and mass-dissipating, and to some extent, it can reduce the application of cefdinir.

Trial design {8}

This trial is a Principle Investigator-initiated, three-arm, multicenter, randomized, active-controlled, outcome assessor-blinded, parallel assignment clinical trial in which 306 participants will be assigned to three groups in 1:1:1 ratio with Pugongying alone, cefdinir alone or combination of Pugongying and cefdinir. The investigators plan to allocate a 3-day treatment and 3-day follow-up to participants. Two visits will be scheduled for each participant: baseline, day-3. At the day-6, the investigators will follow the participants up by telephone or Wechat (a social media used in China).

Methods: Participants, interventions and outcomes

Study setting {9}

Participants will be recruited from clinics in three hospitals: Third Affiliated Hospital, Beijing University of Chinese Medicine, Beijing Hospital of Traditional Chinese Medicine, and Tongzhou Maternal & Child Health Hospital of Beijing, which are all located in Beijing, China.

Eligibility criteria {10}

Inclusion criteria

• Lactating women who have intention to breastfeed child;

• Within 72 hours after the onset of symptoms and/or signs (body temperature≧37.2℃ with at least one symptoms, such as red, painful, swollen and hard of part of breast), and the ultrasound examination indicates there is no mammary abscess;

• The body temperature is higher than 37.2° C but lower than 41° C;

• The VAS scores of breast pain (range from 0-10) ≧4;

• Willing and able to comply with protocol requirements and provide informed consent.

Exclusion criteria

• Having other breast disease that hinders or prevents breastfeeding;

• Having taken therapeutic drugs for this episode of acute mastitis;

• Known allergic to penicillin and cephalosporin;

• Participants with mental disorders, seizure disorders, or cognitive dysfunction;

• Presence of any other pre-existing chronic infection requiring medical therapy;

• Having any history of chronic liver disease, or any active lung, heart or renal diseases requiring regular medication.

The three hospitals are equipped with Breast-Disease Clinics and there are enough patients with acute mastitis to ensure the implementation of this trial.

Who will take informed consent? {26a}

The doctors who will obtain Informed Consent From (ICF) from potential trial participants are licensed and have obtained Good Clinical Practice (GCP) certificates in each hospital. All participants should give written ICF prior to participating the study. The doctors should inform the participants of the protocol, objective, rights and interests, possible risks of the study, study confidentiality and related compensation. And the

participants should be assured that they can quit the study any time.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The participants in Pugongying group and cefdinir group will sign another ICF which contains the item about milk samples collection for further genetic analysis. Three milk samples will be collected on the baseline day (day-0) and day-3. All samples will not be preserved.

Interventions

Explanation for the choice of comparators {6b}

The recommended pharmacological measure of acute mastitis is mainly antibiotics.[2, 12] The preferred antibiotics are usually penicillinase-resistant penicillins, such as dicloxacillin or flucloxacillin, or as recommended by local antibiotic sensitivities.[2] Cefdinir is the 3rd generation of cephalosporin. Due to its few adverse events, weak toxicity, broad anti-microbial spectrum and less prone to drug tolerance, it has been widely applied to mastitis treatment in China. Thus, this trial chooses it as active-controlled intervention.

Intervention description {11a}

In clinics, participants will be randomly assigned to the Chinese patent medicine group (CPM), combination of Chinese patent medicine and Antibiotics cefdinir capsule group (CPM & ACC), or Antibiotics cefdinir capsule group (ACC).

For participants in CPM group, Pugongying should be taken 15g three times a day for 3 days. For CPM & ACC participants, Pugongying should be taken 15g three times a day for 3 days and cefdinir should be taken 0.1g three times a day in the first two days. For participants in ACC group, cefdinir should be taken 0.1g three times a day for 3 days.

Pugongying is named as Pugongying Granule in China and produced by Kunming Pharmaceutical Factory co. LTD. The form of the drug is granule, and the participants will take the drug after dissolved. Cefdinir is also named as cefdinir capsule and produced by Astellas Pharma Inc. The form of the drug is capsule, and participants will orally take the capsules. The investigators will follow them up for 3 days after 3-day drug

administration.

All participants will receive education, including dietary, emotional regulation and the knowledge of breastfeeding. The investigators will encourage participants to remove milk effectively.

Criteria for discontinuing or modifying allocated interventions {11b}

The participants with body temperature above 41℃ in the 3-day treatment period will be recommended to withdraw from the trial and receive intravenous drip antibiotics therapy. If the participants have preference for particular intervention and would not like to continue receiving assigned intervention, they can withdraw from the trial at any time. In the above situations, the investigators will try their best to obtain the participants' data when they withdraw from the trial.

During 3-day treatment, if B-ultrasound hints that there is a mammary abscess, the doctor will discuss with the participants and additionally perform the surgery to prevent them from severe complications if necessary. The participants in CPM group with body temperature above 39℃ will be administered by twice dose of Pugongying.

Strategies to improve adherence to interventions {11c}

Before the beginning of enrollment, the doctors will inform them about high recurrence rate of acute mastitis and the necessity of 3-day drugs administration. And the doctors can assess the disease condition by related laboratory tests and examinations on day-3 to ensure the interests of all enrolled participants. Finally, the investigators will distribute 120% intervention drugs and require the participants to return the drugs at day-3.

Relevant concomitant care permitted or prohibited during the trial {11d}

Education, such as dietary, emotional regulation and the knowledge of breastfeeding, and effective milk removal are permitted. Other drugs for treating acute mastitis, such as ibuprofen and probiotic are prohibited.

Provisions for post-trial care {30}

Provisions for post-trial care are not applicable. Laboratory tests, examinations and treatments for concomitant diseases or complications are not provided freely by the sponsor, which will be communicated to the participants as they sign the informed consent.

Outcomes {12}

Primary outcome measures

Primary outcome measures are the common chief complaints which have strong relevance to acute mastitis.

• Resolution of fever: Body temperature will be measured by mercury thermometer and recorded on the prepared card by participants. The temperature reduces to 37.2℃ or more below, assessing as the normal temperature. And the normal temperature lasts for at least 24 hours, considered as fever-resolution. To evaluate onset time and the temperature changing from baseline to the end of 3-day treatment, participants will be encouraged to measure body temperature every 4 hours for 3 days, specifically on 2:00 am, 6:00 am, 10:00 am, 14:00 pm, 18:00 pm, 22:00 pm.

• VAS sores of breast pain: Breast pain will be self-reported by participants and recorded. The VAS is used to assess breast pain. The scale has been tested in the investigator's previous trial. 0 score indicates "no uncomfortable feeling". 1-3 indicates "mild uncomfortable feeling". 4-6 indicates "moderate uncomfortable feeling". 7-10 indicates "severe uncomfortable feeling". To evaluate the changing from baseline to the end of 3-day treatment, participants will assess breast pain every 8 hours for 3 days, specifically measured on 6:00 am, 14:00 pm, 22:00 pm.

• The size of the breast mass: The mass will be manually outlined by outcome assessors with a measurement film which have registered the patent (Patent No. ZL-2010-2-0172672.8). [19]To evaluate the changing from baseline to the end of 3-day treatment, the mass will be measured at baseline and at the end of the treatment, total 2 times.

Secondary outcome measures

• The patency of milk: The outcome will be measured by the outcome assessor. The 0-3 scores are used to describe the patency of milk from no stagnation to severe stagnation. 0 indicates that there is no stagnation with breast and milk spurts out by slightly pressure; 1 indicates mild stagnation and milk flows by more pressure; 2 indicates moderate stagnation and milk flows by much more pressure; 3 indicates there is severe stagnation and no milk flows. To evaluate the changing, the outcome will be evaluated at baseline and at the end of the treatment, total 2 times.

• TCM symptoms scores: The assessment criteria refer to Standard of diagnosis and treatment in TCM symptoms (2016 version, released by State Administration of Traditional Chinese Medicine of the People's Republic of China, http://www.stctcm.com/STCM/LineAnnouncement/899.htm). The criteria are specifically used to assess the holistic physical status of participants and will be measured by outcome assessors. To evaluate the changing, the outcome will be evaluated at baseline and at the end of the treatment, total 2 times.

• White blood cell count: Measured by the routine blood test. To evaluate the changing, it will be tested at baseline and at the end of 3-day treatment, total 2 times.

• Percentage of neutrophil: Measured by the routine blood test. To evaluate the changing, it will be tested at baseline and at the end of 3-day treatment, total 2 times.

• C-reactive protein: Measured by the routine blood test. To evaluate the changing, it will be tested at baseline and at the end of 3-day treatment, total 2 times.

• The quantity of intervention drugs and the incidence of surgery: After 3-day drug administration, the participants will undergo the clinical evaluation at the 2nd visit and the doctor will recommend whether participants need further treatment. If B-ultrasound shows there is a mammary abscess, the doctor will perform surgery, or prescribe cefdinir or Pugongying based on liquefaction and size of the abscess. Then the investigators will record the quantity of drugs and the incidence of surgery.

• Relapse of acute mastitis: After 3-day treatment, the investigators will follow the participants up for another 3 days to figure out the incidence of acute mastitis relapse. The investigators will call the participants to inquiry their conditions (body temperature and breast pain).

• Safety assessments: To assess the safety of the interventions, the investigators will perform the following tests on participants at baseline and the end of 3-day treatment: routine blood, liver and renal function and electrocardiography. All abnormal values are defined based on reference values.

Participant timeline {13}

Table 1 shows the participant timeline (Please see Table 1 at the end of the document).

Sample size {14}

We analyze all available data from the pilot study on breast-pain VAS scores in lactating women with acute mastitis (unpublished) in Third Affiliated Hospital of Beijing University of Chinese Medicine, and the suggestions from the practitioners to calculate sample size. In this trial, sample size formula in the 4th edition clinical epidemiology is used as reference.[20] In terms of sample size, there is in excess of a 95% power and a (2-side) 10% significance level in detecting treatment differences. The standard deviations are 0.81 in CPM, 0.76 in CPM & ACC, 0.9 in ACC, respectively. The means are 3.55 in CPM, 3.10 in CPM & ACC, 3.34 in ACC, respectively.

$$n = \frac{\Psi^2\left(\sum_{j=1}^{k} \sigma_j^2/k\right)}{\sum_{j=1}^{k} \left(\overline{X}_j - \overline{X}\right)^2/(k-1)}$$

As a result, $\sum_{j=1}^{k}\left(\overline{X}_j - \overline{X}\right)^2 = (3.55-3.33)^2 + (3.34-3.33)^2 + (3.10-3.33)^2 = 0.1014$

$\sum_{j=1}^{k}\sigma_j^2 = 0.81^2 + 0.90^2 + 0.76^2 = 2.0437$

$\Psi_{0.05,0.10,2,\infty} = 2.52$. Bring the results into the formula above, $n = \frac{2.52^2(2.0437/3)}{0.1014/2} \approx 85$. Considering 20% attrition rate, the sample size of each group is 102 and 306 patients will be recruited in total.

Recruitment {15}

The costs of intervention drugs (Pugongying and cefdinir), laboratory tests (routine blood, routine urine) and examinations (breast B-ultrasound and electrocardiogram) will be provided by the sponsor.

Assignment of interventions: allocation

Sequence generation {16a}

The sequence of randomization (1:1:1) will be generated by JHX with a computer program (Excel).

Concealment mechanism {16b}

The randomized number and allocation details will be sealed in opaque envelopes.

Implementation {16c}

JHX will generate the allocation sequence. The doctors who in clinics will enroll participants. And the investigators (e.g. JHX and XYJ) will assign participants to interventions.

Assignment of interventions: Blinding

Who will be blinded {17a}

The trial is an outcome assessor-blinded, data collector-blinded and data analyst-blinded study. Treatment allocations will be concealed from the data analysts by group 1, 2 and 3. The data-collectors (e.g. CG) and outcome assessors (e.g. nurses) blinded about intervention allocations will record the data and evaluate the mass size, patency of milk, TCM symptoms and relapse. Participants preference can have minor influence on body temperature, white blood cell count, the percentage of neutrophil and C-reactive protein.

Procedure for unblinding if needed {17b}

Not applicable. In this trial, participants and doctors will not be blinded, therefore there is no unblinding procedure.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The investigators (JHX, XYJ) have studied for the use of measurement films at The People's Hospital of Liaoning Province on 5th May 2019. XHP, YYF, XYJ and JHX have implemented the project 'The clinical effects of Shaoyao Gualou Gancao decoction combined with Xiaozhong Zhitong patches on the initial stage of acute mastitis: A randomized control trial (unpublished)' and have a good understanding of acute mastitis-related measurement methods and data collection. JHX and XYJ have trained the outcome assessors and data collectors in three hospitals and will not participate in these works. Laboratory tests will be performed in clinical laboratory of each hospital. All abnormal values are defined based on reference values.

Plans to promote participant retention and complete follow-up {18b}

During intervention period and follow-up period, the investigators will communicate with all enrolled participants by telephone or Wechat to obtain the information of the participants' conditions (e.g. body temperature, breast pain). If the participants discontinue or deviate from the study, the investigators will persuade them to receive laboratory tests and examinations to assess their disease conditions and protect their interests.

Data management {19}

All data will be input and checked by two statisticians using EpiData 3.1.

Confidentiality {27}

All participants' personal information will be confidential to the extent permitted by Chinese laws. The samples of enrolled participants will be identified by study numbers rather than their name. Unless the permission is obtained, information that identifies individuals will not be disclosed to anyone other than members of the study group. The investigators, the supervisor appointed by CFH, the ethics committee and CFDA are allowed to access participants' medical records related to the study to ensure the authenticity and accuracy of the data, but other individual information will not be shared. Case report forms (CRF) will be reserved in cabinet unless investigators allow to open. Electronic data will be input according to the study number and accessed under the permission of investigators. When the results of this study are published, no information about the participants will be disclosed.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Four blood, two urine and three milk samples will be collected on the baseline day (day-0) and day-3. Blood samples will be utilized in laboratory tests, including routine blood test, liver and kidney function test. Blood and urine samples will not be saved. All abnormal values will be evaluated based on reference values.

Milk samples will be collected by the investigator (XYJ) in sterile conditions. Then they will be storage in -80 ℃ refrigerator and will be transported to Beijing Major Biomedical Technology Co., Ltd in drikold environment

for further genetic analysis. All samples will not be preserved.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analysis will be conducted by Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine. The statistician (not in authorship) will be blinded from the intervention allocations. SPSS 25.0 statistical software packages will be used to analyze the data. Prior to all analyses, a detailed statistical analysis protocol is developed.

Continuous variables will be expressed as median and standard deviations. Three groups will be compared using Analysis of Variance (ANOVA) or Kruskal Wallis test, as appropriate, based on the data distribution. Two groups will be compared using Least Significant Difference (LSD) if there is significant differences between three groups. Dichotomous variables will be expressed as "yes" or "no". Groups will be compared using the chi-square or Fisher's exact test, as appropriate, based on the expected counts. Participants characteristics and past history will be reported and compared between groups. Descriptive statistics will be presented to describe the trial results. A two-sided $P < 0.05$ will be considered statistically significant.

Interim analyses {21b}

Not applicable. The interim analyses are not planned to conduct.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable. Additional analyses are not planned to conduct.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The intention-to-treat (ITT) population is defined as the patients who are randomized and receive at least one treatment session. The per-protocol (PP) population is defined as the patients who complete the study and do not have major protocol violations. All analyses will be based on the ITT population and the PP population. The result of the ITT analysis will be compared with that of the PP analysis to check whether the results are consistent.[21]

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The data can be available by the corresponding author with reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

CFH will be responsible for quality control and the management will comply with the Administrative Measures of Capital's Funds for Health Improvement and Research published by Beijing Health Commission of the People’s Republic (2017 version). The sponsor will commission the third party to monitor the trial avoiding interest conflicts.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data monitoring committee is not applicable. The data will be monitored by the sponsor.

Adverse event reporting and harms {22}

Any serious adverse events will be reported to the principle investigator within 24 hours and recorded in CRF to analyze the relationship between events and intervention. The serious adverse events will be reported to 2018 Capital's Funds for Health Improvement and Research following GCP guidelines.

Frequency and plans for auditing trial conduct {23}

The sponsor will randomly audit some clinical trials and commission the third party to conduct the audit procedures to avoid interest conflicts.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Important protocol amendments will communicate with enrolled trial participants, investigators, ethical committees of Beijing University of Chinese Medicine Third Affiliated Hospital and the sponsor. And then the

investigators will update the protocol on ClinicalTrials.gov.

Dissemination plans {31a}

We will put up a poster and Wechat post via public account to disseminate this trial.

Discussion

The results of this trial are expected to provide convincing evidence that Pugongying is effective and safety for alleviating manifestations of lactating women with acute mastitis, and they could reduce application of cefdinir in clinical practice.

As we know, milk is not sterile and has a wide range of microbiome which has important health implications.[22, 23] And the relationship of microbiome in milk is in a dynamic equilibrium. The application of antibiotics may induce dysbiosis of milk microbiome.[24] In TCM theory, “vital qi” is a collective designation for all normal function of the human body and the abilities to maintain health, including the abilities to self-regulation, adaptation to the environment, resistance against pathogens and self-recovery from illness, and “pathogenic qi” specifies various pathogenic factors. The occurrence of infectious diseases is the result of internal and external factors’ interactions. Therefore, strengthening body resistance to eliminate pathogenic factors is fundamental therapeutic principle. In microbiology researches, the bacterial communities maintaining the stability, quantities and orders of microbiome are considered as “vital qi”. If the balance is disturbed inducing the dysbiosis of milk, mircobiological colonization resistance and immunity can decline generating “pathogenic qi”. Based on the hypothesis, the treatment of infectious diseases should focus on the biological antagonism of microbiome and then eliminate the pathogenic factors.[25] And the intervention, Pugongying can work both theoretically.

World health organization (WHO) provides a handbook for mothers, and ABM (The Academy of Breastfeeding Medicine Protocol Committee) also publishes the clinical protocol. The recommendations include pharmacological and non-pharmacological interventions, but they do not include TCM which effectively resolves the symptoms of acute mastitis in practice. Pugongying belongs to Chinese patent medicine. Chinese patent medicine has satisfactory characteristics, such as definite benefit response,

guaranteed safety assessment, and it is convenient to taking, carrying and storage. Proving the effectiveness of Pugongying will be helpful to the generalization of TCM. However, there is not enough evidence for Pugongying based on methodology rigorous clinical trial. In this trial, we conduct a multicenter, randomization, outcome assessor-blinded, parallel assignment clinical trial, with a large sample size to ensure power.

There are some limitations of this trial. First, the outcomes of this trial may not be sufficient to evaluate the effectiveness and safety of Pugongying from all angles in the treatment of acute mastitis. However, the core outcome set of mastitis is not available. We try to assess the manifestations of acute mastitis based on clinical experience. Second, we do not use double-blinded design and this may lead to performance bias. But the outcomes measures except the scores of breast pain, are either objective indicators or outcome assessor-evaluation outcomes. The preference of participants and investigators is minimal. Third, the title is "Effects of Chinese herbal medicine Pugongying for reducing the application of antibiotics in breastfeeding women with acute mastitis", but the intervention of this trial is Pugongying which may be not enough to represent Chinese patent medicine. We hope that this trial can preliminarily confirm the effectiveness of Pugongying which is the most representative Chinese patent medicine for the treatment of acute mastitis, and it can be fundamental evidence for future research.

Trial status

Protocol version is version-1 in May 2018. The recruitment began on August 19th 2019 and will be completed approximately on December 31st 2020.

Abbreviations

ABM: The Academy of Breastfeeding Medicine Protocol Committee

ACC: Antibiotics Cefdinir Capsules group

ANOVA: Analysis of Variance

CFH: Capital's Funds for Health Improvement and Research

CFDA: China Food and Drug Administration

CPM: Chinese Patent Medicine group

CPM & ACC: Combination of Chinese Patent Medicine and Antibiotics Cefdinir Capsules group

GCP: Good Clinical Practice

ICF: Informed Consent From

ITT: Intention-to-treat

LSD: Least Significant Difference

PP: Per-protocol

TCM: Traditional Chinese Medicine

VAS: Visual Analogue Scale

WHO: World health organization

Declarations

- Acknowledgements
- Authors' contributions
- Funding
- Availability of data and material
- Ethics approval and consent to participate
- Consent for publication
- Competing interests
- Authors’ information (optional)

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associates. Special thanks to all participants in this study.

Authors' contributions {31b}

XHP as the Principle Investigator, conceived the study and led the proposal.

XYJ contributed to the study design, drafted the manuscript and participated in the study implementation.

CLL assisted in clinical trial registration and participated in the protocol development.

JPL was the lead methodologist of this trial.

JHX contributed to development of the proposal and participated in the manuscript.

YYF participated in the study design and study implementation.

CG assisted in the manuscript.

All authors discussed, read, revised the manuscript, and all approved the final manuscript.

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Availability of data and materials {29}

After this study is completed, the final trial dataset and statistical codes will be available from the corresponding authors upon reasonable request, except for participants' personal information.

Ethics approval and consent to participate {24}

Ethics approval of the study has been obtained from the Ethical Committee of Third Affiliated Hospital of Beijing University of Chinese Medicine (number BZYSY-SFKTPJ-1) and Beijing Hospital of Traditional Chinese Medicine (number 2019BL02-028-02) according to Chinese law. Written, informed consent to participate will be obtained from all participants. An additional file shows ethics approval in more details (see Additional file 2).

Consent for publication {32}

Not applicable. There is no individual personal data in this manuscript.

Competing interests {28}

The authors declare that they have no competing interests.

Authors' information (optional)

Participant Timeline

Table 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	**0**	**0**	***Day-1***	***Day-2***	***Day-3***	***Day-6***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
CPM group			◆—	—	—◆	
ACC group			◆—	—	—◆	
CPM / ***CPM & ACC group***			◆—	—	—◆	
ACC			◆—	—◆		
ASSESSMENTS:	X				X	
Body temperature		X	X	X	X	X

Breast-pain VAS scores		X	X	X	X	X
The area of breast mass		X			X	
The patency of milk		X			X	
The scores of TCM symptoms		X			X	
White blood cell count		X			X	
The percentage of neutrophil		X			X	
C-reactive protein		X			X	
Relapse						X
Surgery incidence						X
Quantity of additional drugs						X
Safety assessment	X				X	

Note: CPM- Chinese Patent Medicine group; CPM & ACC- combination of Chinese Patent Medicine and Antibiotics Cefdinir Capsules group; ACC- Antibiotics Cefdinir Capsules group.

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