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A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial

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ABSTRACT

Introduction

Nipple fissure and nipple pain are common complaints among breastfeeding mothers. Studies found mupirocin was effective in preventing and treating infections of damaged nipple and nipple pain. Acidic fibroblast growth factor (aFGF) plays an important role in wound healing. However, current evidence on the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of well-designed randomised controlled trials on this topic. The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin alone for nipple fissure and nipple pain in breastfeeding women.

Methods and analysis

This study is a randomised, double-blind, single-centre, parallel-group clinical trial. A total of 120 breastfeeding women with nipple fissure and nipple pain will be randomly assigned to either mupirocin plus aFGF group or mupirocin plus placebo group according to a computer-generated random allocation sequence. The treatment period lasts for 14 days. The primary outcome is nipple pain intensity measured using the Visual Analogue Scale. Secondary outcome measures include time to complete nipple pain relief, changes in the Nipple Trauma Score, time to complete healing of nipple trauma, quality of life measured using the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire, and adverse events.

Ethics and dissemination

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001). We plan to publish our research findings on a peer-reviewed academic journal and disseminate these findings on international conferences.

Trial registration number: ChiCTR1800017248

Strengths and limitations of this study:

- This is the first randomised controlled trial to investigate the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women.
- The investigators, patients, pharmacist and outcome assessor are all blinded.
- The generalisability of the results is limited as it is a single-centre trial.
- No cost-effectiveness analysis will be performed.

INTRODUCTION

Breastfeeding is the most recommended way of feeding for new babies under the age of six months[1]. Studies found multiple benefits of breastfeeding to both mother and bady. Breastfeeding is associated with lower risks of gastrointestinal diseases and respiratory diseases in infants[1]. It also brings long-term health benefits to mothers including reduced risks of developing breast cancer, anxiety, and type 2 diabetes[1-3].

Nipple fissure and nipple pain are common complaints among breastfeeding mothers[4,5]. The incidence of nipple fissure and nipple pain during breastfeeding varies from 34% to 96%[5]. Some of the possible causes of nipple fissure or nipple pain include poor infant positioning or latch, prolonged lactation episode, high frequency of feedings, use of nipple shields, breast engorgement and lack of nipple exposure to light and air, etc[5,6]. Traumatic nipples may result in important implications including infants' deprivation of breast milk benefits and considerable stress and dissatisfaction in mothers[7].

Medical management of nipple fissure and nipple pain includes pharmacotherapy (oral or for external use) against bacterial or fungal infections and non-pharmacological interventions such as glycerine, lanolin, peppermint oil, and nipple protectors[5,7,8]. Also, study found educating mothers on proper positioning and latching effectively prevented the incidence and recurrence of nipple fissure and nipple pain[8]. However, no optimal treatment has been identified among the many options of preventative and curative treatments for traumatic nipples or nipple pain[5,7].

Wounded nipples are easily infected with bacteria[9-10]. Studies also found a close association between bacterial infections and nipple pain[10-11]. Mupirocin, a type of antibiotics, could be used for skin infection caused by bacteria[12]. Findings from a few studies suggest that mupirocin alone or in combination with other drugs was effective against infection of damaged nipples and nipple pain[9,13]. Moreover, oral

mupirocin is rapidly metabolized, thus lowering the risk of causing adverse effects in the nursing baby[9].

The process of skin repair involved in the healing of nipple trauma is regulated by a variety of cell growth factors. A review indicated that fibroblast growth factors (FGFs) play an important role in wound healing[14]. FGFs could promote wound healing through stimulating proliferation and differentiation of endothelial cells and fibroblasts and facilitating regeneration of granulation tissues[15,16]. They have been widely used for skin repair following burns, ulcers, skin transplantation, and other types of injuries[17].

Both acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) belong to the FGF family[18]. As acidification is commonly observed in the wounded skin area[19], aFGF is supposed to be more beneficial than bFGF to the healing of wounds. In evidence of the hypothesis, significantly shorter time to complete healing (P=0.035) was observed in skin burn patients receiving aFGF than patients in the bFGF group in a multi-centre clinical research[20].

To our knowledge, current clinical evidence on the efficacy of safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of rigorously-designed randomised controlled trials on this topic.

The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin plus placebo for nipple fissure and nipple pain in breastfeeding women.

METHODS AND ANALYSIS

This protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[21]. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) with a unique ID ChiCTR1800017248. The registration information is available at http://www.chictr.org.cn/showproj.aspx?proj=29278.

Study design

This study is a randomised, double-blind, single-centre, parallel-group clinical trial.

Study setting

Study participants will be recruited from the inpatient and outpatient departments of the galactophore department of Tianjin Central Hospital of Gynecology Obstetrics. Patient recruitment will start in August 2018 and we plan to finish the study by December 2019. A flow diagram is presented in figure 1.

Several strategies will be used to promote patient recruitment, including posting recruitment advertisement on the hospital's official website and exhibiting posters at conspicuous places in the hospital. Telephone consultation service will be provided for patients with interests. Screening of potential participants will be carried out by a trial nurse previously trained of the informing and consenting process.

Participant recruitment

Inclusion criteria

1. Lactating women aged 18 and beyond;
2. Giving birth to their first baby;
3. Two weeks and longer postpartum;
4. Presenting macroscopically detectable nipple trauma or complaining of perceived nipple pain;
5. Full-term pregnancy;
6. Exclusive breastfeeding;
7. No current use of soother and milk bottle for the baby, and nipple protectors for the mother[22];
8. Voluntarily giving informed consent.

Exclusion criteria

1. Women with diagnosed chronic diseases including diabetes, mental disorders, autoimmune diseases and severe anemia;
2. Women suffering from diseases or conditions affecting breastfeeding, including infectious mastitis, ductal infections, flat or depressed nipples, nipple or subareolar abscess, and fungal infection on breast;
3. Previous use of pharmacotherapy for nipple fissure and pain;
4. Allergy to aFGF or mupirocin (At screening, an investigator will perform a skin allergy test by applying the investigational drugs on the forearm of the patient and ask her to observe and report any response within the following 24 hours. Allergy to the investigational drugs will be detected in the presence of allergic reactions);
5. Infants suffering from tongue or tooth disorders.

Interventions

Experimental interventions

Participants randomly assigned to the experimental group will be administered mupirocin plus aFGF treatment during lactation for a consecutive of 14 days, three times daily. The combined treatment includes two steps. First, the breastfeeding mother sprays aFGF on the affected nipple at a dose of 100 IU/cm^2 to ensure complete coverage of the nipple. Second, mupirocin ointment will be lightly and

evenly applied to the same area following the absorption of the spray liquid. Hand washing and nipple cleaning are required before drug use and breastfeeding.

Comparator interventions

Patients in the control group will be provided with mupirocin and aFGF placebo, and will be required to follow the same treatment regimen as in the experimental group.

Mupirocin oinment is manufactured by the Sino-American Tianjin Smith Kline & French Laboratories Ltd. Company. Each gram of the mupirocin oinment contains 20 miligrams of its major active ingrediant mupirocin in a polyethylene glycol base.

Both aFGF and its placebo are in the form of a freeze-dried powder manufactured by the Shanghai WanXing Biology Pharmaceuticals Company. The agent is packaged 25,000 U per tube, containing 2 milliliter of freeze-dried powder. Each time prior to use, the powder needs to be soluted in 0.9% sodium chloride. The aFGF agent and its placebo are indistinguishable from each other in appearance, package, and dosage form[18].

Women in both groups will be given face-to-face instructions on breastfeeding techniques and hygiene as well as an educational pamphlet to take home. To test the mothers' uptake of the pre-study education and ensure consistency, they will be asked to nurse her baby in the face of a female investigator, thus allowing her newly learned skills to be evaluated[8].

The use of sedative drugs and other pharmacotherapy for nipple fissure and pain are prohibited throughout the study period.

The participants are instructed to discontinue treatment if they experience allergic reactions or exacerbation of condition during the study period and report to the investigator immediately. When necessary, anti-allergy treatment will be provided. Infants developing diarrhea, skin rashes, milk rejection, and mouth ulcers during the study will be referred to a professional pediatrician. If necessary, breastfeeding will be discontinued.

Outcome measurements

Primary outcome

The primary outcome is nipple pain intensity measured using the Visual Analogue Scale (VAS) at baseline, and on Day 3, Day 7 and Day 14 during the treatment period[22,23]. The VAS provides a range of scores from 0 to 10, indicating "no pain" to "the most intense pain".

Secondary outcomes

The secondary outcome measures include:

1. Time to complete nipple pain relief is the time taken from baseline to the day when the VAS score is reduced to 0.
2. Changes in the Nipple Trauma Score

The Nipple Trauma Score (NTS) will be used to measure the extent and depth of nipple trauma, which ranges between 0 and 5[22,23]. (See Table 1)

Table 1 Explaination of the ratings for the Nipple Trauma Score

Score	Definition
0	No microscopically visible skin changes
1	Erythema or edema or a combination of both
2	Superficial damage, with or without scab formation, to less than 25% of the nipple surface
3	Superficial damage, with or without scab formation, to more than 25% of the nipple surface
4	Partial-thickness wound, with or without scab formation, affecting less than 25% of the nipple surface
5	Partial-thickness wound, with or without scab formation, affecting more than 25% of the nipple surface

3. Time to complete healing of nipple trauma is time taken from baseline to the day when the NTS decreased to 0.
4. Quality of life

Quality of life will be meansured using the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire. The patient-reported questionaire contains 41 items, providing a total score ranging from 0 to 30. Higher scores indicate better quality of life[24].

Safety outcomes

Any adverse event and reaction observed in both the mother and infant will be recorded. These could be perceived feelings of burning, pricking or tickling on the skin of the nipples, or allergic rash reported by the breastfeeding mother, and diarrhea, rash, milk rejection, and dental ulcer observed in the infant.

Measurement items and time points of data collection

The participants' information and outcome measurements will be collected on five time points, which are on the day of screening, at baseline, and on Day 3, Day 7 and Day 14 during the treatment period. A study flowchart specifying the time schedule for enrollment, intervention, data collection, and participant visits is

presented in Table 2.

Patients visiting the outpatient clinic or from the maternity ward will be first screened against the inclusion and exclusion criteria. Potentially eligible participants will be informed of the aim and content of the research, schedule of visits, risks and benefits involved, and the rights and obligations of the participants prior to being asked to give written consent. The recruiting investigators will be trained in informing and consenting patients before the study kicks off to ensure the patients clearly understand the above information.

On the day following the screening visit (Day 0), participants will be randomly assigned to either the experimental or the control group and required to report the following information.

- For the breastfeeding mothers: age, marital status, family income per year, education, number of pregnancy, history of allergy, exclusive or mixed beastfeeding, previous use of pharmacotherapy for nipple fissure and pain, history of chronic diseases, current use of nipple protectors, complication with other breast diseases affecting nursing, VAS score, NTS and MAPP-QOL score.
- For infants: weight at birth, gestational age, current age (months), presence of oral diseases, and current use of pacifiers or milk bottle.

Evaluation and recording of the VAS score, NTS and MAPP-QOL score will be repeated on Day 3, Day 7 and Day 14 during the treatment period.

The use of concomitant drugs such as sedative agents and other therapies for nipple fissure and pain will be recorded. Any adverse event will be recorded and followed-up until the participant returns to normal.

All outcomes will be measured blindly by an assessor who is trained and tested before performing the trial, in order to promote consistency of outcome measurement.

The participants will be well informed that it is their right to withdraw at any time from the study. Participants could also be asked to discontinue treatment in the case of serious adverse events or severe violation of the approved protocol. Treatment compliance and safety will be monitored daily through telephone communication in the absence of face-to-face meetings. The explainations for participant withdrawal and drop-out will be sought and recorded. Whenever possible， the VAS score and NTS of these patients will be collected through telephone call.

Sample size

We hypothesized based on previous research[23] that the average pain intensity is 1 point in the experimental group and 2 in the control group, both with a standard mean difference of 1.5 point. The sample size of this study was calculated using the PASS 2011 software. A total of 120 participants, 60 in each group, are required to

generate possible statistical difference beteen groups, with a significance level of 0.05，90% confidence, and an estimated drop-out rate of 20%.

Randomization

Block randomization will be used in the present trial with a block size of 4. A statistician independent of the investigators generated a random allocation sequence using a computer software. The statistician will be informed through telephone call if a patient is enrolled, and he will assign a unique identification code to the patient and let the investigator and the pharmacist know the code. Then the patient will be assigned to either the experimental or the control group according to the pre-defined allocation schedule.

Allocation concealment

The investigational drugs are packaged in sealed, opaque boxes of the same size and appearance. Each box is labelled with a unique identifier corresponding to a random number in the allocation sequence before the study commences. The pharmacist dispenses drug to the patient according to the identifier assigned to her and provide instructions on the dosage and dosage regimen of the investigational drugs.

Blinding

In this study, the investigators, the patients, the pharmacist and the outcome assessor are all blinded. In the case of serious adverse event, the investigator will acquire the patient's allocation information from the statistician.

Data management

A case report form (CRF) was composed before the study began. Each variable is carefully coded, preparing data for auditing and statistical analysis.

The patients' general information will be recorded in the CRF by the responsible investigator, whereas patient-reported information will be documented in the CRF by the patient, and there are some parts of the CRF to be completed by the outcome assessor.

We will adopt a double-entry and double-check approach to data management. All the steps involved in data management will be independently conducted by two data administrators using the Epidata software. If any inconsistency is identified in the data-entry or logic check, the investigators will be contacted for further information and clarification.

The participants' identification information (name, telephone, home address, etc) will not be entered into the data management software to protect privacy. The participant's identification code is the unique identifier for a patient in the dataset.

After data checking is done, the final version of dataset will be kept on a locked Compact Disc (CD). The statistician may have access to the complete dataset upon formal written application to the data administrator.

Harm

Any occurance of adverse event needs to be documented in detail, including information on the starting point of symptom appearing, patient symptoms, severity, duration of the condition, any management administered and the final outcome, etc. In the case of a serious adverse event, the investigatior is responsible for informing the sponsor and data monitoring committee immediatedly after he/she learned of the event. The sponsor is responsible for contacting the statistician for the allocation information of the participant and informing the investigator of her assignment in a timely manner. The investigator will take whatever medical measures necessary to remedy harms to the participants happened during participation in the study.

Auditing

A clinical monitor will visit to the study site every two weeks to check how the study has progressed. Important points to check include if the investigators has conducted study as per protocol, how many patients have been screened and how many have been enrolled, and if all consenting participants have signed the informed consent form. Also, the CRFs will be checked for correctness and consistency with source documents. The monitor will evaluate if the investigators have filled in the CRF and other essential documents in a timely manner, and if errors have been corrected and the corrections been signed and dated. Moreover, the monitor needs to make sure any drop-out and adverse event is elaborately recorded.

Data monitoring

A data monitoring committee (DMC) independent of the research investigators will be established to monitor and evaluate safety data throughout the study, serious adverse events, in particular. While the trial is ongoing, DMC members have access to original data but are blinded of participant allocation. One principal role of the DMC is to timely provide the sponsor with written recommendation about the necessity to discontinue a trial following discussion and assessment of safety data.

Statistical analysis

We will use the SPSS 22.0 software for statistical analysis and perform an Intention-To-Treat (ITT) analysis. A p value of less than 0.05 is considered statistically significant. For quantitative data, if they follow normal distribution, the mean value and standard deviation will be used to describe treatment effect. The t-

test will be performed to investigate between-group difference, and the paired t-test for within-group difference. If the quantitative data do no follow normal distribution, the median value and interquartile range will be used to express treatment effect. In this case, the Mann-Whitney U test will be used to check between-group differences, and the Wilcoxon test for within-group variations. For qualitative data, percentage or the incidence rate of event is used to describe effect size, and the chi-square test is used for examing between-group differences.

We did not plan subgroup analysis or adjustment analysis in advance. However, proper statistical adjustment approaches (e.g. covariance analysis, Cox regression analysis) will be adopted in the presence of baseline variations between groups.

Amendments

In case of any amendment to the present protocol, revisions will be submitted to the Ethics Review Committee and DMC. The revisions, reason for making such revisions, the date and the new version number will be specified in the final report.

ETHICS AND DISSEMINATION

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001).

We plan to publish our research findings on a peer-reviewed academic journal and disseminate these findings on international conferences. Trial participants, healthcare professionals and the public may get to know the results of our research by reading the published paper. The full protocol, participant-level dataset and statistical code will be available by contacting the authors after the final report is published.

Participant confidentiality and data protection

Patient data will be kept strictly confidential. After database locking, all statistics will be eliminated of any patient identification information (i.e., name, home address) before entering into statistical analysis.

Patient and public involvement

Patients and/or public were not involved.

Discussion

Currently, there is no standard and optimal treatment for nipple fissure and pain in breastfeeding mothers. The antibiotic mupirocin is useful against superficial skin infections while aFGF facilitates the repair of skin injury. Because bacterial infections are commonly observed in traumatic nipples, we made the hypothesis that combination therapy is more effective than mupirocin alone in the management of this

condition. Findings of this study may provide evidence for the new and probably better treatment option for nursing mothers suffering from nipple fissure and pain.

Contributors: XL and JZ made substantial contributions to the conception and design of the study. XL and JZ wrote the manuscript drafts. RF made significant revisions to the manuscript. All authors read, amended and approved the final manuscript.

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Competing interests: None declared.

Ethics approval: The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001).

Patient consent: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Reference:

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Table 2 Time schedule of participant enrollment, interventions, assessments and visits

	Activity/assessment	Study period				
		-1	0	T1	T2	T3
		Prestudy Screening/ consent (day -1)	Prestudy baseline/ randomisation (day 0)	Study visit 1 (day 3)	Study visit 2 (day 7)	Study visit 3 (day 14)
Enrollment	Eligibility screen	X				
	Informed consent	X				
	Randomisation		X			
	Characteristic		X			
	Medical history		X			
Intervention	Mupirocin plus aFGF		☆———	———	———	☆
	Mupirocin plus placebo		★———	———	———	★
Assessment	Visual analogue scale		X	X	X	X
	Nipple Trauma Score		X	X	X	X
	MAPP-QOL		X	X	X	X
	Time to complete nipple pain relief			X	X	X
	Time to complete healing of nipple trauma			X	X	X
	Adverse events			X	X	X

☆ Experimental group; ★ Control group;

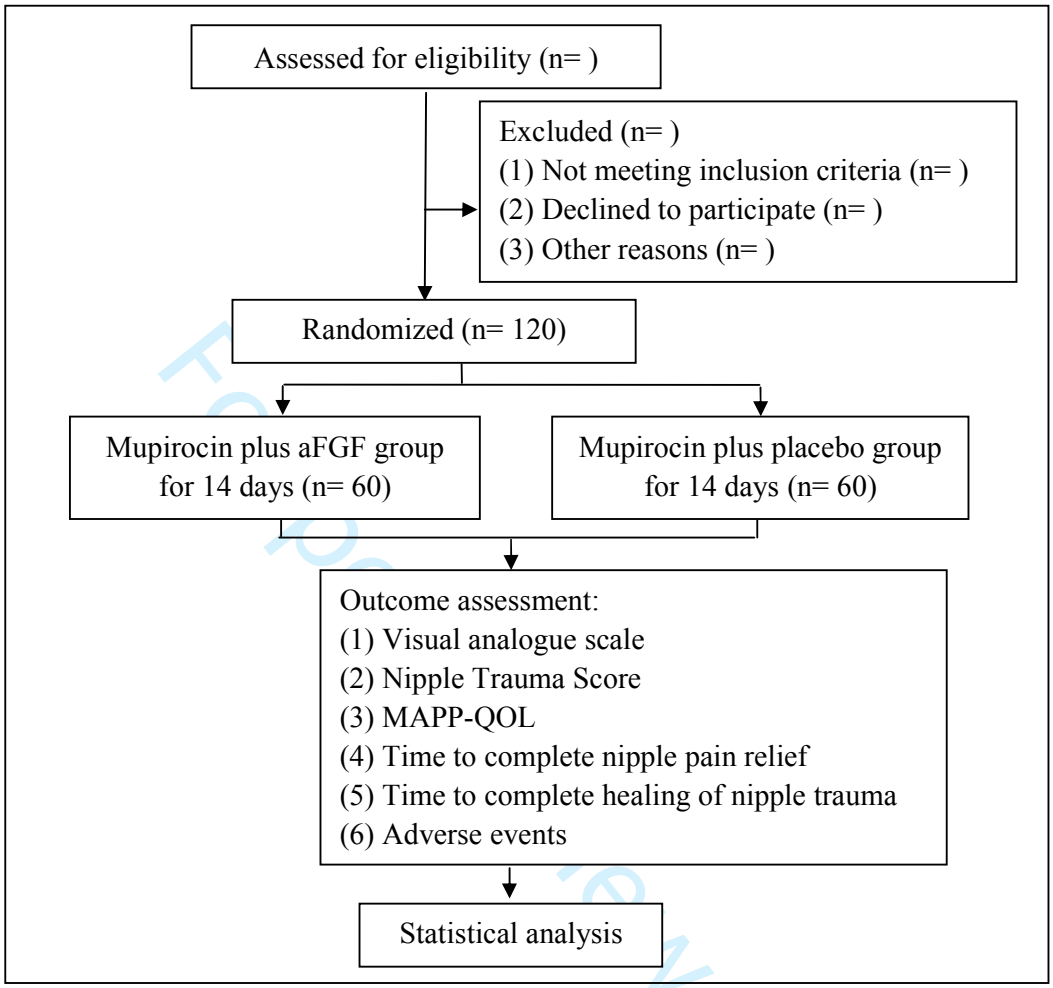

Figure 1 Flow diagram

SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**3**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**3**
Protocol version	**3**	**Date and version identifier**	**No**
Funding	**4**	**Sources and types of financial, material, and other support**	**11**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,11**
	5b	**Name and contact information for the trial sponsor**	**1**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**11**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**9**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**2,3**
	6b	**Explanation for choice of comparators**	**2,3**
Objectives	**7**	**Specific objectives or hypotheses**	**3**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**3**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**3,4**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**4**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**4,5**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**5**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**5**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**5**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**5,6**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**6,7**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**7,8**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**4**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**8**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**8**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**8**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**8**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**9**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**6,7**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**6,7**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8,9
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9,10
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	9
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized	7

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	No
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the tri	9,10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	8,9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	No
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	No

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A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial

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A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial

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ABSTRACT

Introduction

Nipple fissure and nipple pain are common complaints among breastfeeding mothers. Studies found mupirocin was effective in preventing and treating infections of damaged nipple and nipple pain. Acidic fibroblast growth factor (aFGF) plays an important role in wound healing. However, current evidence on the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of well-designed randomised controlled trials on this topic. The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin alone for nipple fissure and nipple pain in breastfeeding women.

Methods and analysis

This study is a randomised, double-blind, single-centre, parallel-group clinical trial. A total of 120 breastfeeding women with nipple fissure and nipple pain will be randomly assigned to either mupirocin plus aFGF group or mupirocin plus placebo group according to a computer-generated random allocation sequence. The treatment period lasts for 14 days. The primary outcome is nipple pain intensity measured by the Visual Analogue Scale at Day 14 during the treatment period. Secondary outcome measures include time to complete nipple pain relief, changes in the Nipple Trauma Score, time to complete healing of nipple trauma, quality of life measured by the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire, and adverse events.

Ethics and dissemination

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001). We plan to publish our research findings on a peer-reviewed academic journal and disseminate these findings on international conferences.

This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) with a unique ID ChiCTR1800017248.

Strengths and limitations of this study:

- This is the first randomised controlled trial to investigate the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women.
- The investigators, patients, pharmacist and outcome assessor are all blinded.
- The generalisability of the results is limited as it is a single-centre trial.
- No cost-effectiveness analysis will be performed.

INTRODUCTION

Exclusive breastfeeding is recommended for the first six months after birth and then infants should be continued breastfeeding into the second year and beyond[1-3]. Some researches have suggested that there are multiple benefits of breastfeeding to both mother and bady. Breastfeeding is associated with lower risks of gastrointestinal diseases and respiratory diseases in infants[4]. It also brings long-term health benefits to mothers including reduced risks of developing breast cancer and type 2 diabetes[4-6].

Nipple fissure and nipple pain are common complaints among breastfeeding mothers[7,8]. Patients may experience one or both of the nipple fissure and nipple pain. A study found that the incidence of nipple fissure ranged from 29% to 76%[9]. Another study showed that the incidence of nipple pain varied between 34% and 96%[10]. Some of the possible causes of nipple fissure or nipple pain include poor infant positioning, prolonged lactation, high frequency of feedings, engorgement of breast and lack of nipple exposure to light and air, etc[8,11,12]. The damaged nipple may lead to breastfeeding cessation[13].

Medical management of nipple fissure and nipple pain includes pharmacotherapy (oral or for external use) against bacterial or fungal infections and non-pharmacological interventions such as glycerine, lanolin, peppermint oil, and nipple protectors[8,10,13-15]. Also, a study found educating mothers on proper positioning and latching effectively prevented the incidence and recurrence of nipple fissure and nipple pain[10]. A systematic review showed that it was inconclusive whether interventions for nipple trauma in breastfeeding mothers were effective[9]. A 2014 Cochrane systematic review showed that there was insufficient evidence to recommend any intervention for the treatment of nipple pain[8].

Damaged nipples are easily infected with bacteria, Candida or other microorganisms[14,16,17]. A study found a close association between bacterial infections

and nipple pain[16]. A prospective study found that 54% of breastfeeding women were infected by staphylococcus aureus[18]. Mupirocin, a type of antibiotic, is used for skin infections caused by bacteria, such as staphylococcus aureus [16,19]. A study suggests that mupirocin is effective against infection of damaged nipples[14]. The mupirocin ointment is usually used sparingly and so the infant is unlikely to ingest a significant amount. Moreover, oral mupirocin is rapidly metabolized, thus lowering the risk of causing adverse effects in the nursing baby[14]. A clinical trial showed that mupirocin was generally well tolerated in infants[20].

The process of skin repair involved in the healing of nipple trauma is regulated by a variety of cell growth factors. A review indicated that fibroblast growth factors (FGFs) played an important role in wound healing[21]. FGFs could promote wound healing through stimulating proliferation and differentiation of endothelial cells and fibroblasts and facilitating regeneration of granulation tissues[22,23]. They have been widely used for skin repair following burns, ulcers, skin transplantation, and other types of injuries[24].

Both acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) belong to the FGF family[25]. As the acidification is commonly observed in the wounded skin area[26], aFGF is supposed to be more effective than bFGF for the healing of wounds. A randomised controlled trial showed that the time to complete healing in aFGF group was significantly shorter (P=0.035) than bFGF group in patients with skin burns[27].

To our knowledge, current clinical evidence on the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of rigorously-designed randomised controlled trials on this topic.

The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin plus placebo for nipple fissure and nipple pain in breastfeeding women.

METHODS AND ANALYSIS

This protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[28]. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) with a unique ID ChiCTR1800017248. The registration information is available at http://www.chictr.org.cn/showproj.aspx?proj=29278.

Study design

This study is a randomised, double-blind, single-centre, parallel-group clinical trial.

Study setting

Study participants will be recruited from the inpatient and outpatient departments of the galactophore department of Tianjin Central Hospital of Gynecology Obstetrics. There are more than 10,000 infants born per year in this hospital. More than 10,000 women attend this clinic. Patient recruitment will start in August 2018 and we plan to finish the study by December 2019. A schematic diagram is presented in Figure 1.

Several strategies will be used to promote participant recruitment, including posting recruitment advertisement on the hospital's official website and exhibiting posters at conspicuous places in the hospital. Telephone consultation service will be provided for patients who are interested in this study. Screening of potential participants will be carried out by a trial nurse previously trained of the informing and consenting process.

Participant recruitment

Inclusion criteria

1. Lactating women aged 18 and beyond;
2. Giving birth to their first baby;
3. Presenting macroscopically detectable nipple fissure and complaining of perceived nipple pain in the first 6 months postpartum;
4. Full-term pregnancy defined as the gestation has lasted 39 to 41 weeks;
5. Exclusive breastfeeding defined as the practice of only giving an infant breast-milk for the first 6 months of life[29];
6. Women suffering from Staphylococcus aureus colonization;
7. No current use of soother and milk bottle for the baby, and nipple protectors (such as nipple shields and breast shells) for the mother[30];
8. Voluntarily giving informed consent.

Exclusion criteria

1. Women with diagnosed chronic diseases, for example, diabetes, mental disorders, autoimmune diseases and severe anemia;
2. Women suffering from diseases or conditions affecting breastfeeding, including infectious mastitis, ductal infections, flat or inverted nipples, nipple or subareolar abscess, and fungal infection on breast;
3. Previous use of pharmacotherapy for nipple fissure and pain;
4. Allergy to aFGF or mupirocin (At screening, an investigator will perform a skin allergy test by applying the investigational drugs on the forearm of the patient and ask her to observe and report any response within the following 24 hours. Allergy to the investigational drugs will be detected in the presence of allergic reactions);
5. Infants suffering from tongue or tooth disorders, such as history of ankylogossia;

6. The use of sedative drugs.

Interventions

Experimental interventions

Participants randomly assigned to the experimental group will be administered mupirocin plus aFGF treatment three times daily for 14 days. The combined treatment includes two steps. First, the breastfeeding mother sprays aFGF on the affected nipple at a dose of 100 IU/cm^2 to ensure complete coverage of the nipple. Second, mupirocin ointment will be lightly and evenly applied to the same area following the absorption of the spray liquid. Participants should wash hands and clean nipples gently before the use of drugs and breastfeeding.

Comparator interventions

Patients in the control group will be provided with mupirocin and aFGF placebo, and will be required to follow the same treatment regimen as in the experimental group.

Mupirocin ointment is manufactured by the Sino-American Tianjin Smith Kline & French Laboratories Ltd. Company. Each gram of the mupirocin oinment contains 20 milligrams of its major active ingredient mupirocin in a polyethylene glycol base.

The aFGF is in the form of a spray manufactured by the Shanghai WanXing Biology Pharmaceuticals Company. The agent contains 2 milliliter of freeze-dried powder (25,000 U per tube) soluted in 10 milliliter of 0.9% sodium chloride solution. The placebo includes only 10 milliliter of 0.9% sodium chloride solution. The aFGF agent and its placebo are indistinguishable from each other in appearance, package, and dosage form[25].

Women in both groups will be given face-to-face instructions on breastfeeding techniques and hygiene as well as an educational pamphlet to take home. To test the mothers' uptake of the pre-study education and ensure consistency, they will be asked to nurse her baby in the face of a female investigator experienced in providing the breastfeeding support, thus allowing her newly learned skills to be evaluated[10].

The use of sedative drugs and other pharmacotherapy for nipple fissure and pain is prohibited throughout the study period. If participant's pain is unresolved after the period of data collection is complete, we will prescribe the painkiller based on the patient's preference.

The participants are instructed to discontinue the treatment if they experience allergic reactions or an exacerbation of the condition during the study period and report to the investigator immediately. When necessary, anti-allergy treatment will be provided. Infants developing diarrhea, skin rashes, milk rejection, and mouth ulcers during the study will be referred to a pediatrician.

Outcome measurements

Primary outcome

The primary outcome is nipple pain intensity measured by the Visual Analogue Scale (VAS) on Day 14 during the treatment period[31,32]. The VAS consists of a ruler marking a range of scores from 0 to 10 in increments of 1, where 0 represents "no pain" and 10 represents "the most intense pain" [31]. The difference of mean scores between groups will be evaluated.

Secondary outcomes

The secondary outcome measures include:

1. Time to complete nipple pain relief

Time to complete nipple pain relief is the time taken from baseline to the day when the VAS score is reduced to 0. If the woman still has nipple pain at Day 14, time to complete nipple pain relief will be marked as a missing value. We will calculate the incidence of complete nipple pain relief.

2. Changes in the Nipple Trauma Score

The Nipple Trauma Score (NTS) will be used to measure the extent and depth of nipple trauma, which ranges between 0 and 5[30,31] (See Table 1). A study showed that testing of NTS revealed a high interobserver reliability of 0.88[31]. The nipple trauma will be evaluated by a dermatoscope.

Table 1 Explaination of the ratings for the Nipple Trauma Score

Score	Definition
0	No microscopically visible skin changes
1	Erythema or edema or a combination of both
2	Superficial damage, with or without scab formation, to less than 25% of the nipple surface
3	Superficial damage, with or without scab formation, to more than 25% of the nipple surface
4	Partial-thickness wound, with or without scab formation, affecting less than 25% of the nipple surface
5	Partial-thickness wound, with or without scab formation, affecting more than 25% of the nipple surface

3. Time to complete healing of nipple trauma

Time to complete healing of nipple trauma is time taken from baseline to the day when the NTS decreased to 0. If the woman still has nipple trauma at Day 14, time to complete healing of nipple trauma will be marked as a missing value. We will calculate the incidence of complete healing of nipple trauma.

4. Quality of life

Quality of life will be measured by the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire[33]. The patient-reported questionaire contains 41 items, providing a total score ranging from 0 to 30. Higher scores indicate better quality of life[33]. The difference of mean scores between groups will be evaluated.

Safety outcomes

Any adverse event and reaction observed in both the mother and infant will be recorded. These could be perceived feelings of burning, pricking or tickling on the skin of the nipples, or allergic rash reported by the breastfeeding mother, diarrhea, rash, milk rejection, and dental ulcer observed in the infant. A data monitoring committee (DMC) will be established to monitor and evaluate safety data throughout the study.

Measurement items and time points of data collection

The participants' information and outcome measurements will be collected on five time points, which are on the day of screening, at baseline, and on Day 3, Day 7 and Day 14 during the treatment period. A study flowchart specifying the time schedule for enrolment, intervention, data collection, and participant visits is presented in Table 2.

Patients visiting the outpatient clinic or from the maternity ward will be first screened against the inclusion and exclusion criteria. Potentially eligible participants will be informed of the aim and content of the research, schedule of visits, risks and benefits involved, and the rights and obligations of the participants prior to being asked to give written consent. The recruiting investigators will be trained in informing and consenting patients before enrolling participants to ensure the patients clearly understand the above information.

On the day following the screening visit (Day 0), participants will be randomly assigned to either the experimental or the control group. Date collection will include the following information.

- For the breastfeeding mothers: age, marital status, family income per year, education, VAS score, NTS and MAPP-QOL score.
- For infants: current age (months).

The VAS score, NTS and MAPP-QOL score will be measured repeatedly on Day 3, Day 7 and Day 14 blindly by an assessor trained and tested before performing the trial in order to promote consistency of the outcome measurement. The explanations for participant withdrawal and drop-out will be sought and recorded by an assessor. Treatment compliance and safety will be monitored daily through the face-to-face interview when patients visit the clinic or telephone communication in the absence of face-to-face meetings. Any adverse event will be recorded and followed-up until the

participant returns to normal by a senior physician (Rui Feng).

Table 2 Time schedule of participant enrolment, interventions, assessments and visits

	Activity/assessment	Study period				
		-1	0	T1	T2	T3
		Prestudy Screening/ consent (day -1)	Prestudy baseline/ randomisation (day 0)	Study visit 1 (day 3)	Study visit 2 (day 7)	Study visit 3 (day 14)
Enrolment	Eligibility screen	X				
	Informed consent	X				
	Randomisation		X			
	Characteristic		X			
Intervention	Mupirocin plus aFGF		☆———	———	———	☆
	Mupirocin plus placebo		★———	———	———	★
Assessment	Visual analogue scale (VAS) for measuring nipple pain		X	X	X	X
	Nipple Trauma Score (NTS)		X	X	X	X
	MAPP-QOL		X	X	X	X
	Time to complete nipple pain relief			X	X	X
	Time to complete healing of nipple trauma			X	X	X
	Adverse events			X	X	X

☆ Experimental group; ★ Control group;

Sample size

We hypothesised that the average pain intensity measured by VAS is 1 point in the experimental group and 2 in the control group, both with a standard mean difference of 1.5 point based on previous research[31]. A sample size of 49 in each group was estimated with a significance level of 0.05 and a power of 90% by the PASS 2011 software. In view of a drop-out rate of 20%, a total of 120 participants, 60

in each group, are required to generate possible statistical difference beteen groups.

Randomisation

Block randomisation will be used with a block size of 4. A statistician independent of the investigators will generate a random allocation sequence by a computer software. When a patient is eligible, the investigator will assign a unique identifier to the patient based on the random allocation sequence. Then the patient will be assigned to either the experimental or the control group.

Allocation concealment

The investigational drugs are packaged in sealed, opaque boxes of the same size and appearance. Each box is labelled with a unique identifier corresponding to a random number in the allocation sequence before the study commences. The pharmacist dispenses drugs to the patient according to the identifier and provide instructions on the dosage and dosage regimen of the investigational drugs.

Blinding

In this study, the investigators, the patients, the pharmacist and the outcome assessor are all blinded. In the case of serious adverse event, the investigator will acquire the patient's allocation information from the statistician.

Data management

A paper case report form (CRF) is composed before the study commences. Each variable is carefully coded for the auditing and statistical analysis.

The patients' general information will be recorded in the CRF by the responsible investigator, whereas the patient-reported information will be documented in the CRF by the patient, and there are some parts of the CRF to be completed by the outcome assessor.

We will adopt a double-entry and double-check approach to data management. All the steps involved in data management will be independently conducted by two data administrators using the Epidata software. If any inconsistency is identified in the data-entry or logic consistence check, the investigators will be contacted for further information and clarification.

The participants' identification information (name, telephone, home address, etc) will not be entered into the data management software to protect the privacy. The participant's identification code is the unique identifier for a patient in the dataset. After data checking is done, the final version of the dataset will be kept on a locked Compact Disc (CD). The statistician may have access to the complete dataset upon formal written application to the data administrator.

Harm

Any occurance of adverse event needs to be documented in detail, including information on the starting point of symptom appearing, patient symptoms, severity, duration of the condition, any management administered and the final outcome, etc. In the case of a serious adverse event, the investigatior is responsible for informing the DMC and contacting the statistician for the allocation information of the participant immediatedly after he/she learned of the event. A senior physician (Rui Feng) will take whatever medical measures necessary to remedy harms to the participants happened in the study. We will pay for out-of-pocket expenses if the woman or infant has a adverse reaction requiring treatment.

Auditing

A clinical monitor will visit to the study site every two weeks to check how the study has progressed. Important points to check include if the investigators has conducted study as per the protocol, how many patients have been screened and how many have been enrolled, and if all eligible participants have signed the informed consent form. Also, the CRFs will be checked for correctness and consistency with source documents. The monitor will evaluate if the investigators have filled in the CRF and other essential documents in a timely manner, and if errors have been corrected and the corrections been signed and dated. Moreover, the monitor needs to make sure any drop-out and adverse event is elaborately recorded.

Data monitoring

The DMC independent of the research investigators will be established to monitor and evaluate safety data throughout the study, serious adverse events, in particular. The DMC is composed of clinicians with expertise in obstetrics and gynecology, and a biostatistician independent of this trial. While the trial is ongoing, DMC members have access to original data but are blinded of participant allocation. If the investigator reports an adverse event, the members of DMC will hold a meeting to evaluate it. One principal role of the DMC is to timely provide the investigator with the written recommendation about the necessity to discontinue a trial following discussion and assessment of safety data.

Statistical analysis

We will perform an Intention-To-Treat (ITT) analysis by the SPSS 22.0 software. P value of less than 0.05 is considered statistically significant. For quantitative data, if they follow the normal distribution, the mean value and standard deviation will be used to describe treatment effects. Otherwise, the median value and interquartile range will be used to express treatment effects. For binary variables, the percentage or

incidence rate is used to describe effect size. The baseline variations between groups will be evaluated by t-test or Mann-Whitney U test. If the baseline variables are similar between groups, the t-test will be used to investigate between-group difference and the paired t-test for within-group difference for quantitative data following the normal distribution, the Mann-Whitney U test for between-group difference and the Wilcoxon test for within-group difference for quantitative data following the non-normal distribution. For binary variables, the chi-square test will be used for examing between-group difference. When baseline variables are various between groups, proper statistical adjustment approaches (e.g. covariance analysis, Cox regression analysis) will be adopted.

Amendments

In case of any amendment to the present protocol, revisions will be submitted to the Ethics Review Committee and DMC. The revisions, reason for making such revisions, the date and the new version number will be specified in the final report.

ETHICS AND DISSEMINATION

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics on January 22, 2018 (Approval No. 2018KY001).

We plan to publish our research findings on a peer-reviewed academic journal and disseminate these findings on international conferences. Trial participants, healthcare professionals and the public may get to know the results of our research by reading the published paper. The full protocol, participant-level dataset and statistical code will be available by contacting the authors after the final report is published.

Participant confidentiality and data protection

Patient data will be kept strictly confidential. After the database is locked, any patient identification information (such as name, home address) will be eliminated before performing the statistical analysis.

Patient and public involvement

Patients and/or public were not involved.

Discussion

Currently, there is no standard and optimal treatment for nipple fissure and pain in breastfeeding mothers. The mupirocin is useful against superficial skin infections while aFGF can facilitate the repair of the skin injury. Because bacterial infections are commonly observed in traumatic nipples, we made the hypothesis that combination

therapy is more effective than mupirocin alone in the management of this condition. Findings of this study may provide evidence for the new and probably better treatment option for nursing mothers suffering from nipple fissure and pain.

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Competing interests: None declared.

Ethics approval: The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001).

Patient consent: Not applicable.

Provenance and peer review: Not commissioned; externally peer reviewed.

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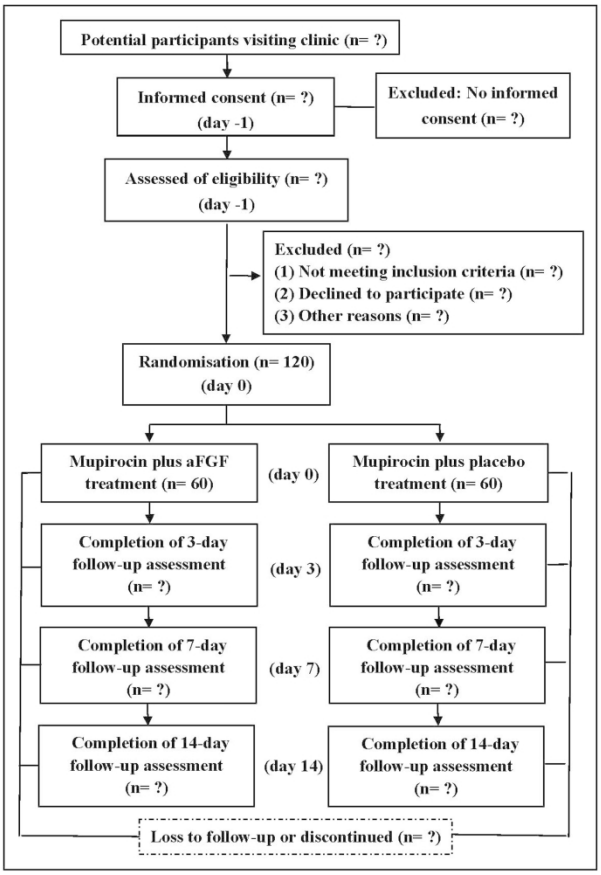
Figure legends:

Figure 1: A schematic diagram of enrolment, interventions, assessments, and visits for participants



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SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**3**
Protocol version	**3**	**Date and version identifier**	**No**
Funding	**4**	**Sources and types of financial, material, and other support**	**12**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,12**
	5b	**Name and contact information for the trial sponsor**	**1**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**12**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**10**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**2,3**
	6b	**Explanation for choice of comparators**	**2,3**
Objectives	**7**	**Specific objectives or hypotheses**	**3**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**3**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**4**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**4,5**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**5**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**5**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**5**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**5**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**6,7**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**7,8**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**8,9**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**4**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**9**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**9**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**9**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**9**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**9**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**7,8**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**7,8**

		protocols	
Data management	**19**	**Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol**	**9**
Statistical methods	**20a**	**Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**	**10,11**
	20b	**Methods for any additional analyses (e.g., subgroup and adjusted analyses)**	**11**
	20c	**Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)**	**10**
Monitoring			
Data monitoring	**21a**	**Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed**	**10**
	21b	**Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial**	**10**
Harms	**22**	**Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct**	**10**
Auditing	**23**	**Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor**	**10**
Ethics and dissemination			
Research ethics approval	**24**	**Plans for seeking REC/IRB approval**	**11**
Protocol amendments	**25**	**Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)**	**11**
Consent or assent	**26a**	**Who will obtain informed consent or assent from potential trial participants or authorized**	**7**

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	No
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the tri	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	9,10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	No
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	No

BMJ Open

A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial

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Primary Subject Heading:	Public health
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A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial

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ABSTRACT

Introduction

Nipple fissure and nipple pain are common complaints among breastfeeding mothers. Studies found mupirocin was effective in preventing and treating infections of damaged nipple and nipple pain. Acidic fibroblast growth factor (aFGF) plays an important role in wound healing. However, current evidence on the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of well-designed randomised controlled trials on this topic. The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin alone for nipple fissure and nipple pain in breastfeeding women.

Methods and analysis

This study is a randomised, double-blind, single-centre, parallel-group clinical trial. A total of 120 breastfeeding women with nipple fissure and nipple pain will be randomly assigned to either mupirocin plus aFGF group or mupirocin plus placebo group according to a computer-generated random allocation sequence. The treatment period lasts for 14 days. The primary outcome is nipple pain intensity measured by the Visual Analogue Scale at Day 14 during the treatment period. Secondary outcome measures include time to complete nipple pain relief, changes in the Nipple Trauma Score, time to complete healing of nipple trauma, quality of life measured by the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire, the frequency of breastfeeding, the rate of breastfeeding discontinuation, weight change in infants and adverse events.

Ethics and dissemination

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001). We plan to publish our research findings on a peer-reviewed academic journal and disseminate

these findings on international conferences.

This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) with a unique ID ChiCTR1800017248.

Strengths and limitations of this study:

- This is the first randomised controlled trial to investigate the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women.
- The investigators, patients, pharmacist and outcome assessor are all blinded.
- The generalisability of the results is limited as it is a single-centre trial.
- No cost-effectiveness analysis will be performed.

INTRODUCTION

Exclusive breastfeeding is recommended for the first six months after birth and then infants should be continued breastfeeding into the second year and beyond[1-3]. Some researches have suggested that there are multiple benefits of breastfeeding to both mother and bady. Breastfeeding is associated with lower risks of gastrointestinal diseases and respiratory diseases in infants[4]. It also brings long-term health benefits to mothers including reduced risks of developing breast cancer and type 2 diabetes[4-6].

Nipple fissure and nipple pain are common complaints among breastfeeding mothers[7,8]. Patients may experience one or both of the nipple fissure and nipple pain. A longitudinal study found that 17% of breastfeeding women experienced nipple fissure and 38% reported nipple pain at 1 month postpartum[9]. A prospective cohort study showed that 58% of women reported nipple damage and 72% experienced nipple pain 1 week after giving birth[10]. A review found that the incidence of nipple fissure ranged from 29% to 76%[11]. Another review showed that the incidence of nipple pain varied between 34% and 96%[12]. Some of the possible causes of nipple fissure or nipple pain include poor infant positioning, prolonged lactation, high frequency of feedings, engorgement of breast and lack of nipple exposure to light and air, etc[8,13,14]. The damaged nipple may lead to breastfeeding cessation[15].

Medical management of nipple fissure and nipple pain includes pharmacotherapy (oral or for external use) against bacterial or fungal infections and non-pharmacological interventions such as glycerine, lanolin, peppermint oil, and nipple protectors[8,12,16-18]. Also, a study found educating mothers on proper positioning and latching effectively prevented the incidence and recurrence of nipple fissure and nipple pain[12]. A systematic review showed that it was inconclusive whether interventions for nipple trauma in breastfeeding mothers were effective[11]. A

2014 Cochrane systematic review showed that there was insufficient evidence to recommend any intervention for the treatment of nipple pain[8].

Damaged nipples are easily infected with bacteria, Candida or other microorganisms[17,19,20]. A study found a close association between bacterial infections and nipple pain[19]. A prospective study found that 54% of breastfeeding women were infected by staphylococcus aureus[21]. Mupirocin, a type of antibiotic, is used for skin infections caused by bacteria, such as staphylococcus aureus [19,22]. A study suggests that mupirocin is effective against infection of damaged nipples[17]. The mupirocin ointment is usually used sparingly and so the infant is unlikely to ingest a significant amount. Moreover, oral mupirocin is rapidly metabolized, thus lowering the risk of causing adverse effects in the nursing baby[17]. A clinical trial showed that mupirocin was generally well tolerated in infants[23].

The process of skin repair involved in the healing of nipple trauma is regulated by a variety of cell growth factors. A review indicated that fibroblast growth factors (FGFs) played an important role in wound healing[24]. FGFs could promote wound healing through stimulating proliferation and differentiation of endothelial cells and fibroblasts and facilitating regeneration of granulation tissues[25,26]. They have been widely used for skin repair following burns, ulcers, skin transplantation, and other types of injuries[27].

Both acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) belong to the FGF family[28]. As the acidification is commonly observed in the wounded skin area[29], aFGF is supposed to be more effective than bFGF for the healing of wounds. A randomised controlled trial showed that the time to complete healing (days) in aFGF group was significantly shorter than bFGF group in patients with skin burns (MD= -2.10, 95% CI: -2.61 to -1.59, P<0.001) [30].

To our knowledge, current clinical evidence on the efficacy and safety of mupirocin plus aFGF for nipple fissure and nipple pain in breastfeeding women is inconclusive due to a lack of rigorously-designed randomised controlled trials on this topic.

The purpose of this study is to test the hypothesis that mupirocin plus aFGF is more effective than mupirocin plus placebo for nipple fissure and nipple pain in breastfeeding women.

METHODS AND ANALYSIS

This protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[31]. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) with a unique ID ChiCTR1800017248. The registration information is available at http://www.chictr.org.cn/showproj.aspx?proj=29278.

Study design

This study is a randomised, double-blind, single-centre, parallel-group clinical trial.

Study setting

Study participants will be recruited from the inpatient and outpatient departments of the breast clinic of Tianjin Central Hospital of Gynecology Obstetrics. There are more than 10,000 infants born per year in this hospital. More than 10,000 women attend this clinic. Patient recruitment will start in August 2018 and we plan to finish the study by December 2019. A schematic diagram is presented in Figure 1.

Several strategies will be used to promote participant recruitment, including posting recruitment advertisement on the hospital's official website and exhibiting posters at conspicuous places in the hospital. Telephone consultation service will be provided for patients who are interested in this study. Screening of potential participants will be carried out by a trial nurse previously trained of the informing and consenting process.

Participant recruitment

Inclusion criteria

1. Lactating women aged 18 and beyond;
2. Giving birth to their first baby;
3. Presenting macroscopically detectable nipple fissure and complaining of perceived nipple pain in the first 6 months postpartum;
4. Full-term pregnancy defined as the gestation has lasted 39 to 41 weeks;
5. Women suffering from Staphylococcus aureus colonization;
6. No current use of nipple protectors (such as nipple shields and breast shells) for the mother[32];
7. Voluntarily giving informed consent.

Exclusion criteria

1. Women with diagnosed chronic diseases, for example, diabetes, mental disorders, autoimmune diseases and severe anemia;
2. Women suffering from diseases or conditions affecting breastfeeding, including infectious mastitis, ductal infections, flat or inverted nipples, nipple or subareolar abscess, and fungal infection on breast;
3. Allergy to aFGF or mupirocin (At screening, an investigator will perform a skin allergy test by applying the investigational drugs on the forearm of the patient and ask her to observe and report any response within the following 24 hours. Allergy to the

investigational drugs will be detected in the presence of allergic reactions);
4. Infants suffering from tongue or tooth disorders, such as history of ankylogossia;

Interventions

Experimental interventions

Participants randomly assigned to the experimental group will be administered mupirocin plus aFGF treatment three times daily for 14 days. The combined treatment includes two steps. First, the breastfeeding mother sprays aFGF on the affected nipple at a dose of 100 IU/cm^2 to ensure complete coverage of the nipple. Second, mupirocin ointment will be lightly and evenly applied to the same area following the absorption of the spray liquid. Participants should wash hands and clean nipples gently before the use of drugs and breastfeeding.

Comparator interventions

Patients in the control group will be provided with mupirocin and aFGF placebo, and will be required to follow the same treatment regimen as in the experimental group.

Mupirocin ointment is manufactured by the Sino-American Tianjin Smith Kline & French Laboratories Ltd. Company. Each gram of the mupirocin oinment contains 20 milligrams of its major active ingredient mupirocin in a polyethylene glycol base.

The aFGF is in the form of a spray manufactured by the Shanghai WanXing Biology Pharmaceuticals Company. The agent contains 2 milliliter of freeze-dried powder (25,000 U per tube) soluted in 10 milliliter of 0.9% sodium chloride solution. The placebo includes only 10 milliliter of 0.9% sodium chloride solution. The aFGF agent and its placebo are indistinguishable from each other in appearance, package, and dosage form[28].

Women in both groups will be given face-to-face instructions on breastfeeding techniques and hygiene as well as an educational pamphlet to take home. To test the mothers' uptake of the pre-study education and ensure consistency, they will be asked to nurse her baby in the face of a female investigator experienced in providing the breastfeeding support, thus allowing her newly learned skills to be evaluated[12].

The use of sedative drugs and other pharmacotherapy for nipple fissure and pain is prohibited throughout the study period. If participant's pain is unresolved after the period of data collection is complete, we will prescribe the painkiller based on the patient's preference.

The participants are instructed to discontinue the treatment if they experience allergic reactions or an exacerbation of the condition during the study period and report to the investigator immediately. When necessary, anti-allergy treatment will be provided. Infants developing diarrhea, skin rashes, milk rejection, and mouth ulcers

during the study will be referred to a pediatrician.

Outcome measurements

Primary outcome

The primary outcome is nipple pain intensity measured by the Visual Analogue Scale (VAS) on Day 14 during the treatment period[33,34]. The VAS consists of a ruler marking a range of scores from 0 to 10 in increments of 1, where 0 represents "no pain" and 10 represents "the most intense pain" [35]. The difference of mean scores between groups will be evaluated.

Secondary outcomes

The secondary outcome measures include:

1. Time to complete nipple pain relief

Time to complete nipple pain relief is the time taken from baseline to the day when the VAS score is reduced to 0. If the woman still has nipple pain at Day 14, time to complete nipple pain relief will be marked as a missing value. We will calculate the incidence of complete nipple pain relief.

2. Changes in the Nipple Trauma Score

The Nipple Trauma Score (NTS) will be used to measure the extent and depth of nipple trauma, which ranges between 0 and 5[32,35] (See Table 1). A study showed that testing of NTS revealed a high interobserver reliability of 0.88[35]. The nipple trauma will be evaluated by a dermatoscope.

Table 1 Explaination of the ratings for the Nipple Trauma Score

Score	Definition
0	No microscopically visible skin changes
1	Erythema or edema or a combination of both
2	Superficial damage, with or without scab formation, to less than 25% of the nipple surface
3	Superficial damage, with or without scab formation, to more than 25% of the nipple surface
4	Partial-thickness wound, with or without scab formation, affecting less than 25% of the nipple surface
5	Partial-thickness wound, with or without scab formation, affecting more than 25% of the nipple surface

3. Time to complete healing of nipple trauma

Time to complete healing of nipple trauma is time taken from baseline to the day when the NTS decreased to 0. If the woman still has nipple trauma at Day 14, time to complete healing of nipple trauma will be marked as a missing value. We will calculate the incidence of complete healing of nipple trauma.

4. Quality of life

Quality of life will be measured by the Maternal Postpartum Quality of Life (MAPP-QOL) questionnaire[36]. The patient-reported questionaire contains 41 items, providing a total score ranging from 0 to 30. Higher scores indicate better quality of life[36]. The difference of mean scores between groups will be evaluated.

5. Outcomes associated with the infant feeding

The frequency of breastfeeding, the rate of breastfeeding discontinuation and weight change in infants will be measured during the treatment period.

Safety outcomes

Any adverse event and reaction observed in both the mother and infant will be recorded. These could be perceived feelings of burning, pricking or tickling on the skin of the nipples, or allergic rash reported by the breastfeeding mother, diarrhea, rash, milk rejection, and dental ulcer observed in the infant. A data monitoring committee (DMC) will be established to monitor and evaluate safety data throughout the study.

Measurement items and time points of data collection

The participants' information and outcome measurements will be collected on five time points, which are on the day of screening, at baseline, and on Day 3, Day 7 and Day 14 during the treatment period. A study flowchart specifying the time schedule for enrolment, intervention, data collection, and participant visits is presented in Table 2.

Patients visiting the outpatient clinic or from the maternity ward will be first screened against the inclusion and exclusion criteria. Potentially eligible participants will be informed of the aim and content of the research, schedule of visits, risks and benefits involved, and the rights and obligations of the participants prior to being asked to give written consent. The recruiting investigators will be trained in informing and consenting patients before enrolling participants to ensure the patients clearly understand the above information.

On the day following the screening visit (Day 0), participants will be randomly assigned to either the experimental or the control group. Date collection will include the following information.

- For the breastfeeding mothers: age, marital status, family income per year, education, VAS score, NTS and MAPP-QOL score.
- For infants: current age (months).

The VAS score, NTS and MAPP-QOL score will be measured repeatedly on Day 3, Day 7 and Day 14 blindly by an assessor trained and tested before performing the trial in order to promote consistency of the outcome measurement. The explanations

for participant withdrawal and drop-out will be sought and recorded by an assessor. Treatment compliance and safety will be monitored daily through the face-to-face interview when patients visit the clinic or telephone communication in the absence of face-to-face meetings. Any adverse event will be recorded and followed-up until the participant returns to normal by a senior physician (Rui Feng).

Table 2 Time schedule of participant enrolment, interventions, assessments and visits

	Activity/assessment	Study period				
		-1	0	T1	T2	T3
		Prestudy Screening/ consent (day -1)	Prestudy baseline/ randomisation (day 0)	Study visit 1 (day 3)	Study visit 2 (day 7)	Study visit 3 (day 14)
Enrolment	Eligibility screen	X				
	Informed consent	X				
	Randomisation		X			
	Characteristic		X			
Intervention	Mupirocin plus aFGF		☆——————————☆			
	Mupirocin plus placebo		★——————————★			
Assessment	Visual analogue scale (VAS) for measuring nipple pain		X	X	X	X
	Nipple Trauma Score (NTS)		X	X	X	X
	MAPP-QOL		X	X	X	X
	Time to complete nipple pain relief			X	X	X
	Time to complete healing of nipple trauma			X	X	X
	Outcomes associated with the infant feeding			X	X	X
	Adverse events			X	X	X

☆ Experimental group; ★ Control group;

Sample size

We hypothesised that the reduction in average pain intensity measured by VAS is 1 point in the experimental group and 2 in the control group, both with a standard mean difference of 1.5 point based on previous research[35]. A sample size of 50 in each group was estimated with a significance level of 0.05 and a power of 90% by the PASS 2011 software. In view of a drop-out rate of 20%, a total of 120 participants, 60 in each group, are finally required to generate possible statistical difference beteen groups.

Randomisation

Block randomisation will be used with a block size of 4. A statistician independent of the investigators will generate a random allocation sequence by a computer software. When a patient is eligible, the investigator will assign a unique identifier to the patient based on the random allocation sequence. Then the patient will be assigned to either the experimental or the control group.

Allocation concealment

The investigational drugs are packaged in sealed, opaque boxes of the same size and appearance. Each box is labelled with a unique identifier corresponding to a random number in the allocation sequence before the study commences. The pharmacist dispenses drugs to the patient according to the identifier and provide instructions on the dosage and dosage regimen of the investigational drugs.

Blinding

In this study, the investigators, the patients, the pharmacist and the outcome assessor are all blinded. In the case of serious adverse event, the investigator will acquire the patient's allocation information from the statistician.

Data management

A paper case report form (CRF) is composed before the study commences. Each variable is carefully coded for the auditing and statistical analysis.

The patients' general information will be recorded in the CRF by the responsible investigator, whereas the patient-reported information will be documented in the CRF by the patient, and there are some parts of the CRF to be completed by the outcome assessor.

We will adopt a double-entry and double-check approach to data management. All the steps involved in data management will be independently conducted by two data administrators using the Epidata software. If any inconsistency is identified in the

data-entry or logic consistence check, the investigators will be contacted for further information and clarification.

The participants' identification information (name, telephone, home address, etc) will not be entered into the data management software to protect the privacy. The participant's identification code is the unique identifier for a patient in the dataset. After data checking is done, the final version of the dataset will be kept on a locked Compact Disc (CD). The statistician may have access to the complete dataset upon formal written application to the data administrator.

Harm

Any occurance of adverse event needs to be documented in detail, including information on the starting point of symptom appearing, patient symptoms, severity, duration of the condition, any management administered and the final outcome, etc. In the case of a serious adverse event, the investigatior is responsible for informing the DMC and contacting the statistician for the allocation information of the participant immediatedly after he/she learned of the event. A senior physician (Rui Feng) will take whatever medical measures necessary to remedy harms to the participants happened in the study. We will pay for out-of-pocket expenses if the woman or infant has a adverse reaction requiring treatment.

Auditing

A clinical monitor will visit to the study site every two weeks to check how the study has progressed. Important points to check include if the investigators has conducted study as per the protocol, how many patients have been screened and how many have been enrolled, and if all eligible participants have signed the informed consent form. Also, the CRFs will be checked for correctness and consistency with source documents. The monitor will evaluate if the investigators have filled in the CRF and other essential documents in a timely manner, and if errors have been corrected and the corrections been signed and dated. Moreover, the monitor needs to make sure any drop-out and adverse event is elaborately recorded.

Data monitoring

The DMC independent of the research investigators will be established to monitor and evaluate safety data throughout the study, serious adverse events, in particular. The DMC is composed of clinicians with expertise in obstetrics and gynecology, clinical experts experienced in conducting clinical trials and a biostatistician independent of this trial. While the trial is ongoing, DMC members have access to original data but are blinded of participant allocation. If the investigator reports an adverse event, the members of DMC will hold a meeting to evaluate it. One principal role of the DMC is to timely provide the investigator with the written

recommendation about the necessity to discontinue a trial following discussion and assessment of safety data.

Statistical analysis

We will perform an Intention-To-Treat (ITT) analysis by the SPSS 22.0 software. P value of less than 0.05 is considered statistically significant. For quantitative data, if they follow the normal distribution, the mean value and standard deviation will be used to describe treatment effects. Otherwise, the median value and interquartile range will be used to express treatment effects. For binary variables, the percentage or incidence rate is used to describe effect size. The baseline variations between groups will be evaluated by t-test or Mann-Whitney U test. If the baseline variables are similar between groups, the t-test will be used to investigate between-group difference and the paired t-test for within-group difference for quantitative data following the normal distribution, the Mann-Whitney U test for between-group difference and the Wilcoxon test for within-group difference for quantitative data following the non-normal distribution. For binary variables, the chi-square test will be used for examing between-group difference. When baseline variables are various between groups, proper statistical adjustment approaches (e.g. covariance analysis, Cox regression analysis) will be adopted.

Amendments

In case of any amendment to the present protocol, revisions will be submitted to the Ethics Review Committee and DMC. The revisions, reason for making such revisions, the date and the new version number will be specified in the final report.

ETHICS AND DISSEMINATION

The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics on January 22, 2018 (Approval No. 2018KY001).

We plan to publish our research findings on a peer-reviewed academic journal and disseminate these findings on international conferences. Trial participants, healthcare professionals and the public may get to know the results of our research by reading the published paper. The full protocol, participant-level dataset and statistical code will be available by contacting the authors after the final report is published.

Participant confidentiality and data protection

Patient data will be kept strictly confidential. After the database is locked, any patient identification information (such as name, home address) will be eliminated before performing the statistical analysis.

Patient and public involvement

Patients and/or public were not involved.

Discussion

Currently, there is no standard and optimal treatment for nipple fissure and pain in breastfeeding mothers. The mupirocin is useful against superficial skin infections while aFGF can facilitate the repair of the skin injury. Because bacterial infections are commonly observed in traumatic nipples, we made the hypothesis that combination therapy is more effective than mupirocin alone in the management of this condition. Findings of this study may provide evidence for the new and probably better treatment option for nursing mothers suffering from nipple fissure and pain.

Contributors: XL and JZ made substantial contributions to the conception and design of the study. XL and JZ wrote the manuscript drafts. RF made significant revisions to the manuscript. All authors read, amended and approved the final manuscript.

Funding: This work is funded by the Tianjin Education Commission ‘‘Innovative Team Training Program” (No. TD13-5047). This funding source has no role in the design of this study.

Data sharing: Medical researchers can obtain individual de-identified participant data collected during the trial, study protocol, statistical analysis plan and analytic code immediately following publication for any purpose by contacting the corresponding author.

Competing interests: None declared.

Ethics approval: The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics (Approval No. 2018KY001).

Patient consent: Not applicable.

Provenance and peer review: Not commissioned; externally peer reviewed.

Reference:

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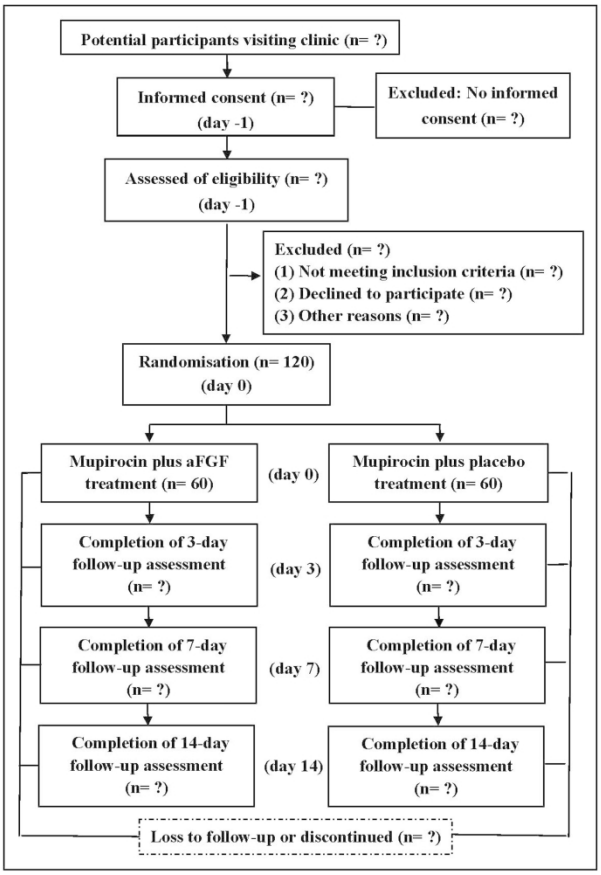
Figure legends:

Figure 1: A schematic diagram of enrolment, interventions, assessments, and visits for participants



210x297mm (300 x 300 DPI)

SPIRIT checklist

Section/Item	Item Number	Description	Reported on page #
Administrative information			
Title	**1**	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym**	**1**
Trial registration	**2a**	**Trial identifier and registry name. If not yet registered, name of intended registry**	**2**
	2b	**All items from the World Health Organization Trial Registration Data Set**	**3**
Protocol version	**3**	**Date and version identifier**	**No**
Funding	**4**	**Sources and types of financial, material, and other support**	**12**
Roles and responsibilities	**5a**	**Names, affiliations, and roles of protocol contributors**	**1,12**
	5b	**Name and contact information for the trial sponsor**	**1**
	5c	**Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**	**12**
	5d	**Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable**	**10**
Introduction			
Background and rationale	**6a**	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**	**2,3**
	6b	**Explanation for choice of comparators**	**2,3**
Objectives	**7**	**Specific objectives or hypotheses**	**3**
Trial design	**8**	**Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority,**	**4**

		exploratory)	
Methods Participants, interventions, and outcomes			
Study setting	**9**	**Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained**	**4**
Eligibility criteria	**10**	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)**	**4,5**
Interventions	**11a**	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**	**5**
	11b	**Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)**	**5**
	11c	**Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)**	**5**
	11d	**Relevant concomitant care and interventions that are permitted or prohibited during the trial**	**5**
Outcomes	**12**	**Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended**	**6,7**
Participant timeline	**13**	**Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended**	**7,8**
Sample size	**14**	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**	**9**

Recruitment	**15**	**Strategies for achieving adequate participant enrollment to reach target sample size**	**4**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	**16a**	**Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions**	**9**
Allocation concealment mechanism	**16b**	**Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned**	**9**
Implementation	**16c**	**Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions**	**9**
Blinding (masking)	**17a**	**Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how**	**9**
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial**	**9**
Data collection, management, and analysis			
Data collection methods	**18a**	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol**	**7,8**
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention**	**7,8**

		protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,10
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	10
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized	7

		surrogates, and how (see item 32)	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	No
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the tri	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	9,10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogate	No
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	No