PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Lv, Xiaofang; Feng, Rui; Zhai, Jingbo

VERSION 1 - REVIEW

REVIEWER	Kimberley Jackson Arthur Labatt Family School of Nursing Western University Canada
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	An argument needs to be made on the link between nipple pain and nipple fissure. Although both are commonly experienced, they are not the same. In fact, many women with fissures do not report significant pain, and conversely, many with severe pain do not have fissures. There are also studies that look specifically at the issue of nipple fissures (and causes) and these need mentioning. You discuss the treatment for nipple fissures and pain, but the mode of treatment will be determined by the cause (eg. Fungal infections will be treated differently from fissures due to mechanical trauma). It is important to be clear that there is a lack of evidence as to what are effective treatments for nipple pain (that is, medical approaches are currently lacking). The issue of safety related to mupirocin use (as it applies to breastfeeding/breastmilk) needs to be more fulsomely explored in the introduction. You do not report taking an intention to treat approach to your analysis. This is needed. Please indicate how you will control for contamination. P. 3, line 4: Please indicate what trial registry this is registered with. P. 3, line 23: I recommend citing the World Health Organization's recommendation for infant feeding. P. 3, line 23: Change "studies found" to "research has suggested that there are…" p. 3, line 27: I don't agree that the literature has sufficiently supported the link between breastfeeding and a reduction anxiety. I suggest removing this claim.

	p. 3, line 31: The range given here is for nipple pain, not for nipple fissure. Please cite the primary studies where they specifically look at nipple fissure (as this is not synonymous with nipple pain). p. 3, line 33: remove “episode” p. 3, line 35: change “traumatic” to “damaged” p. 3, line 35-37: this sentence is awkwardly worded and can be restated more clearly. p. 3, line 44: cite Jackson, K., & Dennis, C-L’s (2017) study in Maternal and Child Nutrition re: lanolin p. 3, line 44: insert “a” before “study” p. 3, line 51: wounded nipples are also easily infected by other microorganisms (eg. Candida). Please include this with appropriate referencing. p. 3, line 54: change “antibiotics” to “antibiotic”, and “could” to “is”, and “infection” to “infections” p. 3, line 55: change “drugs” to “medications” p. 4, line 24: “evidence on the efficacy of safety…” should read “evidence on the efficacy and safety…” p. 5, line 7: change “interests” to “interest in the study” Inclusion criteria: i) is it any detectable trauma? Please make this clear; ii) define full term, in weeks: iii) exclusive according to which classification (eg. Labbok & Krasovek or WHO?); iv) why greater than two weeks postpartum? Most nipple pain and damage occurs in the first 48 hours postpartum. Exclusion criteria: i) for the first exclusion criterion I would suggest saying “for example” instead of “including” – which suggests exclusivity ii) what if women had an infant with ankylogossia but it was repaired? Experimental interventions: I am concerned with the safety of applying a non-tested topical spray to the nipple where infants will be breastfeeding. How will you be certain that the infant will not receive any of this medication inadvertently? Please also be mindful that additional washing/wiping of the nipples can add to nipple trauma and exacerbate nipple pain. Are there any infant trials of oral mupirocin and aFGF? Comparator interventions: what is the placebo? It needs to be 100% safe and inert for infants. p. 6, line 33: the use of sedative drugs needs to be added to your exclusion criteria. p. 6, line 38: how will infant or maternal allergic reaction be assessed? What is the safety protocol? What are the indications for stopping the trial? p. 6, line 51: which version of the visual analogue scale will be used? The continuous line where participants mark an “x” in between 0-10, or will it have numeric indicators (1,2,3…) on it? If the former, how will this be quantified? p. 7, line 6: what if participant’s pain is unresolved after the period of data collection is complete? p. 7, line 9 (and others): i) Psychometrics (reliability/validity) need to be reported on for the population of interest for all the measurement tools; ii) how will nipples be evaluated microscopically?

	p. 7, line 35: what will you be evaluating with respect to quality of life? Difference between groups in mean scores, meeting a cutoff, other? Please clarify. Safety outcomes: how will you know if an adverse event/reaction has occurred? How often will women be contacted to assess for this? What is the safety protocol if an event takes place? Who will pay for out of pocket expenses if the woman or child has a medical reaction requiring treatment? p. 7, line 53: are women not having baseline data collected on the day they consent? Ie., would it not make sense to collect baseline and then days 3, 7, and 14 versus having the additional collection on day of screening? This is a bit confusing. p. 8, lines 19-24: some of the demographic data are part of your exclusion criteria. For example previous use of pharmacology for nipple fissure and parity. These women would be screened out before they would have demographic data collected, correct? Are women not screened before randomization takes place? p. 8, line 30: how will these data be collected? In person (interview), online survey, other? p. 8, line 34: how will participants be "followed up until the participant returns to normal"? Will a referral be made to primary care? Explain. p. 8, 38-47: your maneuver as it is outlined here is quite confusing. Please re-write to increase clarity and transparency as to what will happen, and when, to participants. P 8, 52-54: It is unclear what this means. Average pain intensity on what measurement? The VAS? Numerous other studies that have measured pain among this population of women have reported pain ratings in the moderate to severe range (i.e. 4-6/10 for moderate and 7-10/10 for severe). These numbers seem quite low. To be clear, are you looking for a mean difference of 1.5 points or a change from baseline of 1.5. Please clarify.

REVIEWER	A/Prof Lisa Amir Judith Lumley Centre La Trobe University Australia
REVIEW RETURNED	27-Nov-2018

GENERAL COMMENTS	Abstract Methods Primary outcome – nipple pain intensity – need to say when this is measured. Which time period is the primary outcome? I note that this is missing from the trial registry as well. Introduction First para needs revising – exclusive breastfeeding is recommended for the first six months and then continued breastfeeding into the second year and beyond. The references for the importance (n.b. not "benefits") of breastfeeding are a bit odd. Most authors are citing the 2016 Lancet series (Rollins et al and Victora et al). Second para – needs an epidemiological ref for the prevalence of nipple pain and damage. And need to double check that these refs (5 and 6) do say these are causes of pain and damage – use of nipple shields is usually a result of nipple pain, not a cause. p. 2, line 51. "Wounded nipples" – "damaged nipples" is a better term.

	p. 2, line 52. Ref #11 is about Candida – a fungal infection, not a bacterial infection. Please double check you have used the best reference every time. p. line 57. – check refs 9 and 13 say this. p. 3, line 3. Usually it is stated that the cream is used sparingly and so the infant is unlikely to ingest a significant amount p. 3, line 20. Evidence that aFGF is “more beneficial”? p. 3, line 23. Add that this was a RCT - this is the strength of the study, not that it was multi-centred. Methods p. 3, line 54. What is “galactophore”? p. 3. Study setting. It would be helpful to have more information about feasibility of the trial. How many births at this hospital per year. How many women attend this clinic? Participants are expected to make 4 visits in two weeks – is this feasible? Have women been consulted about this protocol? p. 4, lien 2. “patient recruitment” – should be “participant recruitment”. p. 4, Inclusion criteria #5. Nipple trauma or pain – this seems vague – could someone have nipple damage and not complain of pain? What if someone’s pain score was 1 out 10 for a single feed? They would be eligible according to this. #6. Exclusive breastfeeding – how are you defining this? What if the baby had some formula in first week? Or is currently receiving expressed breast milk only? #7. “nipple protectors” – do you mean nipple shields or breast shells. Exclusion criteris #2. “depressed nipples” – should be “inverted”. #3. Previous pharmacotherapy – even lanolin? What if it was 2 weeks earlier? I think most women would be excluded using these definitions strictly. p. 5, line 30. “female investigator” – more important to say that this person is experienced in providing breastfeeding support. p. 5, line 32. Are you saying that analgesics are not allowed to be used? I don’t think women will agree to this. p. 5, line 41. “Professional” can be deleted. Also the next sentence – why would breastfeeding be discontinued? p. 5, line 52. These are not references for the VAS. And as mentioned earlier – the primary outcome can not be Day 3, 7 and 14. One timepoint must be chosen. p. 6. Time to complete pain relief and healing – what if the woman still has pain and/or damage at day 14? p. 6, Safety outcomes – the DMC should be mentioned here. p. 7, line 12. “kicks off” is too colloquial. p. 7, line 16. “required to report’ is too authoritarian. You can say “Data collection will include…” Proper definitions of infant feeding and other measures are needed. p. 7, line 43. Telephone communication daily is mentioned. The contact points need to be more clearly defined earlier - ? 4 visits and daily phone calls. p. 7, line 53. Is one point difference on a VAS clinically significant? The sample size calculation needs more information – what was the sample size calculated before 20% was added for loss to follow-up? p. 8.. Randomisation – usually drug trials have the medications already labelled according to a randomization plan. p. 8, line 26. Pharmacists are not necessarily female. p. 9. Harm – is aFGF safe for ingestion? Who is the sponsor? p. 9. DMC – who will make up the DMC? When will they meet? p. 10. First para – needs work. You first have to compare groups and make sure the baseline variables are similar, if not you will need to adjust for these. What do you mean “for qualitative data”? p. 10. Ethics – date of approval? p. 11. “Patient consent: Not required” – maybe should be “Not applicable” because you mean for this protocol paper, not the actual trial. Figure 1 Flow chart. Please study the CONSORT examples of flow charts for protocols. The two boxes don’t come together, there should be boxes below and number follow-up at each time-point, and reasons for loss to follow-up, and then how many are analysed in each group. See the 2013 SPIRIT guidelines:

	https://www.bmj.com/content/346/bmj.e7586.full?ijkey=QpAJnYI57zIwVr3&keytype=ref Under “Outcome assessment” – (1) Visual analogue scale. Needs to say “Nipple pain measured by VAS”. Also in Table 2. Readers need to know what the VAS refers to.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Kimberley Jackson

Institution and Country: Arthur Labatt Family School of Nursing, Western University, Canada

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for the opportunity to review this protocol. Interventions addressing nipple pain and nipple trauma are greatly needed. There are some issues with the manuscript that require attention, most notably related to safety. Please see the attached list of issues/questions.

General comments:

An argument needs to be made on the link between nipple pain and nipple fissure. Although both are commonly experienced, they are not the same. In fact, many women with fissures do not report significant pain, and conversely, many with severe pain do not have fissures. There are also studies that look specifically at the issue of nipple fissures (and causes) and these need mentioning. You discuss the treatment for nipple fissures and pain, but the mode of treatment will be determined by the cause (eg. Fungal infections will be treated differently from fissures due to mechanical trauma).

Response:

I agree with your point. Patients may experience one or both of the nipple fissure and nipple pain. In the clinical practice, breastfeeding women with nipple fissure often go to a doctor because of nipple pain. I have mentioned some studies which look specifically at the issue of nipple fissures in the introduction. Indeed, the mode of treatment is determined by the cause. In this study, patients with staphylococcus aureus colonization will be included and treated with mupirocin. I have made the advised changes in the section of “introduction and participant recruitment”.

It is important to be clear that there is a lack of evidence as to what are effective treatments for nipple pain (that is, medical approaches are currently lacking).

Response:

Thanks for your suggestion. A 2014 Cochrane systematic review showed that there was insufficient evidence to recommend any intervention for the treatment of nipple pain. I have made the advised changes in the section of “introduction”.

The issue of safety related to mupirocin use (as it applies to breastfeeding/breastmilk) needs to be more fulsomely explored in the introduction.

Response:

Thanks for your suggestion. A clinical trial showed that mupirocin was generally well tolerated in infants. I have explored the safety of mupirocin, especially in infants in the section of “introduction”.

You do not report taking an intention to treat approach to your analysis. This is needed.

Response:

Thanks for your suggestion. I have reported an intention-to-treat approach in the section of ‘Statistical analysis’.

Please indicate how you will control for contamination.

Response:

Thanks for your suggestion. Hand washing and nipple cleaning are required before drug use and breastfeeding. I have reported these information in the section of “Interventions”.

P. 3, line 4: Please indicate what trial registry this is registered with.

Response:

This study has been registered on the Chinese Clinical Trial Registry (ChiCTR). I have revised this sentence.

P. 3, line 23: I recommend citing the World Health Organization’s recommendation for infant feeding.

Response:

Thanks for your suggestion. I have cited this reference in the first sentence of “introduction”.

P. 3, line 23: Change “studies found” to “research has suggested that there are…”

Response:

Thanks for your suggestion. I have revised this sentence according to your advice.

p. 3, line 27: I don’t agree that the literature has sufficiently supported the link between breastfeeding and a reduction anxiety. I suggest removing this claim.

Response:

Thanks for your suggestion. I have removed this claim.

p. 3, line 31: The range given here is for nipple pain, not for nipple fissure. Please cite the primary studies where they specifically look at nipple fissure (as this is not synonymous with nipple pain).

Response:

Thanks for your suggestions. I have cited some studies where they specifically look at nipple fissure in the section of “introduction”..

p. 3, line 33: remove “episode”

Response:

Thanks for your suggestion. I have removed this word.

p. 3, line 35: change “traumatic” to “damaged”

Response:

Thanks for your suggestion. I have replaced “traumatic” with “damaged”.

p. 3, line 35-37: this sentence is awkwardly worded and can be restated more clearly.

Response:

Thanks for your suggestion. I have revised this sentence according to your advice.

p. 3, line 44: cite Jackson, K., & Dennis, C-L’s (2017) study in Maternal and Child Nutrition re: lanolin

Response:

Thanks for your suggestion. I have cited this reference.

p. 3, line 44: insert “a” before “study”

Response:

Thanks for your suggestion. I have inserted “a” before “study”.

p. 3, line 51: wounded nipples are also easily infected by other microorganisms (eg. Candida). Please include this with appropriate referencing.

Response:

Thanks for your suggestion. I have cited a appropriate reference on Candida.

p. 3, line 54: change “antibiotics” to “antibiotic”, and “could” to “is”, and “infection” to “infections”

Response:

Thanks for your suggestions. I have corrected these words.

p. 3, line 55: change “drugs” to “medications”

Response:

Thanks for your suggestion. I have revised this sentence according to your and other reviewer’s advice.

p. 4, line 24: “evidence on the efficacy of safety…” should read “evidence on the efficacy and safety…”

Response:

Thanks for your suggestion. I have corrected this word.

p. 5, line 7: change “interests” to “interest in the study”

Response:

Thanks for your suggestion. I have corrected this word.

Inclusion criteria: i) is it any detectable trauma? Please make this clear; ii) define full term, in weeks: iii) exclusive according to which classification (eg. Labbok & Krasovek or WHO?); iv) why greater than two weeks postpartum? Most nipple pain and damage occurs in the first 48 hours postpartum.

Response:

Thanks for your suggestions. I have made the advised changes in the section of “Inclusion criteria”. Patients with any macroscopically detectable nipple fissure and complaining of perceived nipple pain will be considered. Recruitment difficulties are commonly encountered in clinical trials. In order to promote adequate enrolment, women suffering from nipple fissure and pain in the first 6 months postpartum will be considered. I have made the advised changes in the section of “Inclusion criteria”. Full-term pregnancy is defined as the gestation has lasted 39 to 41 weeks. Exclusive breastfeeding is defined as the practice of only giving an infant breast-milk for the first 6 months of life according to WHO.

Exclusion criteria: i) for the first exclusion criterion I would suggest saying “for example” instead of “including” – which suggests exclusivity ii) what if women had an infant with ankylogossia but it was repaired?

Response:

Thanks for your suggestions. I have made the advised changes in the section of “Exclusion criteria”. I have replaced “including” with “for example”. Women having an infant with repaired ankylogossia will be excluded.

Experimental interventions: I am concerned with the safety of applying a non-tested topical spray to the nipple where infants will be breastfeeding. How will you be certain that the infant will not receive any of this medication inadvertently? Please also be mindful that additional washing/wiping of the nipples can add to nipple trauma and exacerbate nipple pain. Are there any infant trials of oral mupirocin and aFGF?

Response:

Thanks for your suggestions. A clinical trial showed that mupirocin was generally well tolerated in infants. I have explored the safety of mupirocin, especially in infants in the section of “introduction”. A multicenter randomized controlled trial showed that no adverse drug reactions were found in children with aFGF treatment (Liu Yuchang, Lin Jianning, Li Yazhou. Study on Promotion Effect of Recombinant Human Acidic Fibroblast Growth Factor on Wound Healing in Children by Multicenter Randomized Controlled Trials. China Pharmacist 2015,18(1):77-79). Moreover, women should wash hands and clean nipples gently before drug use and breastfeeding. A data monitoring committee (DMC) independent of the research investigators will be established to monitor and evaluate safety data throughout the study, I have added these information in the section of “Introduction” and “Interventions”.

Comparator interventions: what is the placebo? It needs to be 100% safe and inert for infants.

Response:

Thanks for your suggestions. The placebo includes only 10 milliliter of 0.9% sodium chloride solution.

p. 6, line 33: the use of sedative drugs needs to be added to your exclusion criteria.

Response:

Thanks for your suggestion. I have added the use of sedative drugs in the section of “exclusion criteria”.

p. 6, line 38: how will infant or maternal allergic reaction be assessed? What is the safety protocol? What are the indications for stopping the trial?

Response:

Thanks for your suggestions. The infant or maternal allergic reaction will be assessed by a data monitoring committee (DMC). The safety protocol was described in the section of “Harm and Data monitoring”. DMC will timely provide the investigator with written recommendation about the necessity to discontinue a trial following discussion and assessment of safety data.

p. 6, line 51: which version of the visual analogue scale will be used? The continuous line where participants mark an “x” in between 0-10, or will it have numeric indicators (1,2,3…) on it? If the former, how will this be quantified?

Response:

Thanks for your suggestions. 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”. I have made the advised changes in the section of “Primary outcome”.

p. 7, line 6: what if participant’s pain is unresolved after the period of data collection is complete?

Response:

Thanks for your suggestions. According to our experience, most of breastfeeding mothers with nipple pain are unwilling to take the paregoric in view of potential adverse effects of drugs on infants. 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. I have made the advised changes in the section of “Interventions”.

p. 7, line 9 (and others): i) Psychometrics (reliability/validity) need to be reported on for the population of interest for all the measurement tools; ii) how will nipples be evaluated microscopically?

Response:

Thanks for your suggestions. Testing of NTS revealed a high interobserver reliability of 0.88 (Abou-Dakn M, Fluhr JW, Gensch M, et al. Positive effect of HPA lanolin versus expressed breastmilk on painful and damaged nipples during lactation. Skin Pharmacol Physiol 2011;24:27-35.). The nipple trauma will be evaluated by a dermatoscope. I have made the advised changes in the section of “Secondary outcomes”.

p. 7, line 35: what will you be evaluating with respect to quality of life? Difference between groups in mean scores, meeting a cutoff, other? Please clarify. Safety outcomes: how will you know if an adverse event/reaction has occurred? How often will women be contacted to assess for this? What is the safety protocol if an event takes place? Who will pay for out of pocket expenses if the woman or child has a medical reaction requiring treatment?

Response:

Thanks for your suggestions. The difference of MAPP-QOL mean scores between groups will be evaluated. The 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 by an assessor. A data monitoring committee (DMC) independent of the research investigators will be established to monitor, evaluate and identify adverse drug events or reactions throughout the study, Any adverse event will be recorded and followed-up until the participant returns to normal. We will pay for out-of-pocket

expenses if the woman or infant has a adverse reaction requiring treatment. I have made the advised changes in the section of “Primary outcome”.

p. 7, line 53: are women not having baseline data collected on the day they consent? Ie., would it not make sense to collect baseline and then days 3, 7, and 14 versus having the additional collection on day of screening? This is a bit confusing.

Response:

Thanks for your suggestions. 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. Therefore, baseline data will be collected the next day.

p. 8, lines 19-24: some of the demographic data are part of your exclusion criteria. For example previous use of pharmacology for nipple fissure and parity. These women would be screened out before they would have demographic data collected, correct? Are women not screened before randomization takes place?

Response:

Thanks for your suggestions. I agree with your points. The eligible patient will be randomly assigned to either the experimental or the control group after screening. I have deleted these infromation associated with the screening in the section of “Measurement items and time points of data collection”.

p. 8, line 30: how will these data be collected? In person (interview), online survey, other?

Response:

Thanks for your suggestions. The patients’ general information will be recorded in the paper case report form (CRF) by the responsible investigator, whereas patient-reported information will be documented in the paper CRF by the patient, and there are some parts of the paper 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. I have made the advised changes in the section of “Data management”.

p. 8, line 34: how will participants be “followed up until the participant returns to normal”? Will a referral be made to primary care? Explain.

Response:

Thanks for your suggestions. Any adverse event will be recorded and followed-up until the participant returns to normal by a senior physician (Rui Feng). This doctor will take whatever medical measures necessary to remedy harms to the participants happened in the study. We will not make a referral to primary care. I have made the advised changes in the section of “Measurement items and time points of data collection” and “Harm”.

p. 8, 38-47: your maneuver as it is outlined here is quite confusing. Please re-write to increase clarity and transparency as to what will happen, and when, to participants.

Response:

Thanks for your suggestions. I have made the advised changes in the section of “Measurement items and time points of data collection”.

P 8, 52-54: It is unclear what this means. Average pain intensity on what measurement? The VAS? Numerous other studies that have measured pain among this population of women have reported pain ratings in the moderate to severe range (i.e. 4-6/10 for moderate and 7-10/10 for severe). These numbers seem quite low. To be clear, are you looking for a mean difference of 1.5 points or a change from baseline of 1.5. Please clarify.

Response:

Thanks for your suggestions. The pain intensity was measured by VAS. I read these studies that measured pain among this population of women have reported pain ratings in the moderate to severe range. I think that the cutoff value is too subjective. The parameters in the process of sample size calculation are hypothesized based on a previous trial cited in the section of “Sample size”. I have made the advised changes in the section of “Sample size”.

Reviewer: 2

Reviewer Name: A/Prof Lisa Amir

Institution and Country: Judith Lumley Centre, La Trobe University, Australia

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

2018-025526 protocol

Abstract

Methods

Primary outcome – nipple pain intensity – need to say when this is measured. Which time period is the primary outcome? I note that this is missing from the trial registry as well.

Response:

Thanks for your suggestions. I have made the advised changes in the section of “Abstract”.

Introduction

First para needs revising – exclusive breastfeeding is recommended for the first six months and then continued breastfeeding into the second year and beyond. The references for the importance (n.b. not “benefits”) of breastfeeding are a bit odd. Most authors are citing the 2016 Lancet series (Rollins et al and Victora et al).

Response:

Thanks for your suggestions. I have revised the first paragraph and cited recommended references in the section of “Introduction”.

Second para – needs an epidemiological ref for the prevalence of nipple pain and damage. And need to double check that these refs (5 and 6) do say these are causes of pain and damage – use of nipple shields is usually a result of nipple pain, not a cause.

Response:

Thanks for your suggestions. I have revised the second paragraph and checked related references in the section of “Introduction”.

p. 2, line 51. “Wounded nipples” – “damaged nipples” is a better term.

Response:

Thanks for your suggestion. I have replaced “Wounded nipples” with “damaged nipples”.

p. 2, line 52. Ref #11 is about Candida – a fungal infection, not a bacterial infection. Please double check you have used the best reference every time.

Response:

Thanks for your suggestion. I have checked and deleted this reference.

p. line 57. – check refs 9 and 13 say this.

Response:

Thanks for your suggestions. I have checked and revised related references.

p. 3, line 3. Usually it is stated that the cream is used sparingly and so the infant is unlikely to ingest a significant amount

Response:

Thanks for your suggestions. I have added this sentence in the section of “Introduction”.

p. 3, line 20. Evidence that aFGF is “more beneficial”?

Response:

Thanks for your suggestion. I have revised this sentence.

p. 3, line 23. Add that this was a RCT - this is the strength of the study, not that it was multi-centred.

Response:

Thanks for your suggestion. I have revised this sentence.

Methods

p. 3, line 54. What is “galactophore”?

Response:

The galactophore department is a section of Tianjin Central Hospital of Gynecology Obstetrics. Women with breast-related diseases will go to the doctor in this department.

p. 3. Study setting. It would be helpful to have more information about feasibility of the trial. How many births at this hospital per year. How many women attend this clinic? Participants are expected to make 4 visits in two weeks – is this feasible? Have women been consulted about this protocol?

Response:

Thanks for your suggestions. I have added some information about feasibility of the trial according to your advice. There are more than 10,000 infants born in this hospital per year. More than 10,000 women attend this clinic. We consulted with some women with nipple fissure and nipple pain. They thought that this protocol was feasible.

p. 4, lien 2. “patient recruitment” – should be “participant recruitment”.

Response:

Thanks for your suggestion. I have revised this sentence.

p. 4, Inclusion criteria #5. Nipple trauma or pain – this seems vague – could someone have nipple damage and not complain of pain? What if someone’s pain score was 1 out 10 for a single feed? They would be eligible according to this.

Response:

Thanks for your suggestions. Women with macroscopically detectable nipple fissure and complaining of perceived nipple pain will be considered. I have revised this item.

#6. Exclusive breastfeeding – how are you defining this? What if the baby had some formula in first week? Or is currently receiving expressed breast milk only?

Response:

Thanks for your suggestions. Exclusive breastfeeding is defined as the practice of only giving an infant breast-milk for the first 6 months of life recommended by World Health Organization. I have revised this item.

#7. “nipple protectors” – do you mean nipple shields or breast shells.

Response:

Thanks for your suggestion. The nipple protectors include nipple shields, breast shells, et al. I have revised this item.

Exclusion criteris

#2. “depressed nipples” – should be “inverted”.

Response:

Thanks for your suggestion. I have replaced “depressed” with “inverted”.

#3. Previous pharmacotherapy – even lanolin? What if it was 2 weeks earlier?

I think most women would be excluded using these definitions strictly.

Response:

Thanks for your suggestions. According to our clinical practice, most of breastfeeding women with nipple fissure and pain often take no drugs before going to a doctor in consideration of drug safety in infants. Recruitment difficulties are commonly encountered in clinical trials. In order to promote adequate enrolment, women suffering from nipple fissure and pain in the first 6 months postpartum will be considered. I have made the advised changes in the section of “Inclusion criteria”.

p. 5, line 30. “female investigator” – more important to say that this person is experienced in providing breastfeeding support.

Response:

Thanks for your suggestions. I have revised this sentence according to your advice.

p. 5, line 32. Are you saying that analgesics are not allowed to be used? I don't think women will agree to this.

Response:

Thanks for your suggestions. In the clinical practice, most of breastfeeding women tell us that nipple pain is tolerable and often take no drugs before going to a doctor in consideration of drug safety in infants. In order to avoid cointervention bias, analgesics will be prohibited.

p. 5, line 41. "Professional" can be deleted. Also the next sentence – why would breastfeeding be discontinued?

Response:

Thanks for your suggestions. I have deleted this word "Professional" and the sentence "If necessary, breastfeeding will be discontinued.".

p. 5, line 52. These are not references for the VAS. And as mentioned earlier – the primary outcome can not be Day 3, 7 and 14. One timepoint must be chosen.

Response:

Thanks for your suggestions. I have added references for the VAS. Day 14 will be chosen. I have made the advised changes in the section of "Primary outcome".

p. 6. Time to complete pain relief and healing – what if the woman still has pain and/or damage at day 14?

Response:

Thanks for your suggestions. If the woman still has nipple pain and/or damage at day 14, time to complete nipple pain relief and/or healing will be marked as a missing value. We will calculate the incidence of complete pain relief or healing. I have made the advised changes in the section of "Outcome measurements".

p. 6, Safety outcomes – the DMC should be mentioned here.

Response:

Thanks for your suggestions. I have made the advised changes in the section of "Safety outcomes".

p. 7, line 12. "kicks off" is too colloquial.

Response:

Thanks for your suggestion. I have revised this sentence.

p. 7, line 16. "required to report' is too authoritarian. You can say "Data collection will include…"

Proper definitions of infant feeding and other measures are needed.

Response:

Thanks for your suggestions. I have revised this sentence according to your advice. Some importment measures has been appropriately defined.

p. 7, line 43. Telephone communication daily is mentioned. The contact points need to be more clearly defined earlier - ? 4 visits and daily phone calls.

Response:

Thanks for your suggestions. I have revised these sentences according to your advice in the section of “Measurement items and time points of data collection”.

p. 7, line 53. Is one point difference on a VAS clinically significant? The sample size calculation needs more information – what was the sample size calculated before 20% was added for loss to follow-up?

Response:

Thanks for your suggestions. I have revised these sentences according to your advice in the section of “Sample size”.

p. 8.. Randomisation – usually drug trials have the medications already labelled according to a randomization plan.

Response:

Thanks for your suggestions. I have revised these sentences according to your advice in the section of “Randomization”.

p. 8, line 26. Pharmacists are not necessarily female.

Response:

Thanks for your suggestion. I have revised this sentence according to your advice in the section of “Allocation concealment”.

p. 9. Harm – is aFGF safe for ingestion? Who is the sponsor?

Response:

Thanks for your suggestions. A multicenter randomized controlled trial showed that no adverse drug reactions were found in children with aFGF treatment (Liu Yuchang, Lin Jianning, Li Yazhou. Study on Promotion Effect of Recombinant Human Acidic Fibroblast Growth Factor on Wound Healing in Children by Multicenter Randomized Controlled Trials. China Pharmacist 2015,18(1):77-79). Moreover, Participants will wash hands and clean nipples gently before drug use and breastfeeding. The sponsor refers to the investigator. There is a mistake and I have revised this sentence.

p. 9. DMC – who will make up the DMC? When will they meet?

Response:

Thanks for your suggestions. The DMC is composed of clinicians with expertise in obstetrics and gynecology and a biostatistician independent of this trial. When the investigator reports an adverse event, the members of DMC will hold a meeting to evaluate it. I have made the advised changes in the section of “Data monitoring”.

p. 10. First para – needs work. You first have to compare groups and make sure the baseline variables are similar, if not you will need to adjust for these. What do you mean “for qualitative data”?

Response:

Thanks for your suggestions. The qualitative data refers to the binary variable. I have made the advised changes in the section of “Statistical analysis”.

p. 10. Ethics – date of approval?

Response:

Thanks for your suggestions. The study has gained approval from the Ethics Review Committee of Tianjin Central Hospital of Gynecology Obstetrics on January 22, 2018 (Approval No. 2018KY001). I have made the advised changes in the section of “Ethics and dissemination”.

p. 11. “Patient consent: Not required” – maybe should be “Not applicable” because you mean for this protocol paper, not the actual trial.

Response:

Thanks for your suggestion. I have replaced “Not required” with “Not applicable”.

Figure 1 Flow chart. Please study the CONSORT examples of flow charts for protocols. The two boxes don’t come together, there should be boxes below and number follow-up at each time-point, and reasons for loss to follow-up, and then how many are analysed in each group. See the 2013 SPIRIT guidelines:

https://www.bmj.com/content/346/bmj.e7586.full?ijkey=QpAJnYI57zIwVr3&keytype=ref

Response:

Thanks for your suggestion. I have revised the flow chart according to your advice.

Under “Outcome assessment” – (1) Visual analogue scale. Needs to say “Nipple pain measured by VAS”. Also in Table 2. Readers need to know what the VAS refers to.

Response:

Thanks for your suggestion. I have made the advised changes in the section of “Outcome measurements” and Table 2.

VERSION 2 – REVIEW

REVIEWER	Lisa Amir La Trobe University, Australia
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	I just have a few comments on this revised version of the trial protocol. 1. Exclusion criteria. I am concerned that these are too strict: - exclusive breastfeeding since birth:, e.g. infant may have had formula in hospital for hypoglycaemia and would be excluded, etc. - medications prohibited: most postpartum women take analgesics for pain postbirth for pain relief.

	When I pointed this out, you have said that women don't take medications, but I would recommend checking the feasibility of both of these exclusion criteria before commencing the trial. 2. Referencing has improved, but work is still needed in paragraph 2 of the Introduction. I suggested epidemiology refs were needed for the first sentence about the prevalence of nipple pain and damage, but this was not done. The following sentences refer to a "study"and änother study"- these are both review articles, so should be referred to as review articles, not studies. Ref #12 is a trial of treatment, and not appropriate for the sentence about causes of pain. Is ref #13 appropriate for the last sentence? 3. p. 3. line 20. "significantly shorter"- more meaningful to show the actual difference in time for healing - hours/days? 4. Methods. Study setting. Galactophore is not the right word in English. Is this a breastfeeding clinic? A breast clinic? 5. Outcome measures. A primary reference is needed for the VAS. I can't see a proper description of infant feeding measures. 6. Sample size. Need to add "reduction in" before äverage pain intensity" so the sentence makes sense. You will need to recruit more than 120 participants to allow a 20% loss to follow-up. 20% of 120 = 24. So, 120-24 = 96. Estimated sample size stated as 98. 7. DMC. Usually you would include clinical experts who are also experienced in conducting clinical trials.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Lisa Amir

Institution and Country: La Trobe University, Australia

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

I just have a few comments on this revised version of the trial protocol.

1. Exclusion criteria. I am concerned that these are too strict:

- exclusive breastfeeding since birth:, e.g. infant may have had formula in hospital for hypoglycaemia and would be excluded, etc.

- medications prohibited: most postpartum women take analgesics for pain postbirth for pain relief.

When I pointed this out, you have said that women don't take medications, but I would recommend checking the feasibility of both of these exclusion criteria before commencing the trial.

Response:

Thanks for your suggestions. I agreed with you and I have removed the above items in the section of “inclusion and exclusion criteria”.

2. Referencing has improved, but work is still needed in paragraph 2 of the Introduction.

I suggested epidemiology refs were needed for the first sentence about the prevalence of nipple pain and damage, but this was not done. The following sentences refer to a "study"and änother study"- these are both review articles, so should be referred to as review articles, not studies. Ref #12 is a trial of treatment, and not appropriate for the sentence about causes of pain. Is ref #13 appropriate for the last sentence?

Response:

Thanks for your suggestions. I have added the epidemiological researches about the prevalence of nipple pain and damage. I have replaced "study" with “review” in the following two sentences. I have deleted ref #12 and ref #13, and supplemented appropriate references.

3. p. 3. line 20. "significantly shorter"- more meaningful to show the actual difference in time for healing - hours/days?

Response:

Thanks for your suggestions. I have added the actual mean difference in the time to complete healing (days) and 95% credibility interval.

4. Methods. Study setting. Galactophore is not the right word in English. Is this a breastfeeding clinic? A breast clinic?

Response:

Thanks for your suggestions. I have replaced “Galactophore” with “breast clinic”.

5. Outcome measures. A primary reference is needed for the VAS. I can't see a proper description of infant feeding measures.

Response:

Thanks for your suggestions. I have supplemented appropriate references for the VAS and outcome measures associated with the infant feeding in the section of “Outcome measures”.

6. Sample size. Need to add "reduction in" before äverage pain intensity" so the sentence makes sense. You will need to recruit more than 120 participants to allow a 20% loss to follow-up. 20% of 120 = 24. So, 120-24 = 96. Estimated sample size stated as 98.

Response:

Thanks for your suggestions. I have added "reduction in" before äverage pain intensity". I have consulted with a statistician and revised the estimate of sample size. Before adding the number of patients who loss to follow-up, a total of 100 participants is required. Then, in view of a drop-out rate of 20%, a total of 120 participants (100*1.2=120), 60 in each group, are required finally.

7. DMC. Usually you would include clinical experts who are also experienced in conducting clinical trials.

Response:

Thanks for your suggestions. I have included clinical experts who are also experienced in conducting clinical trials in the section of “Data monitoring”.