Author’s response to reviews

Title: Efficacy of Chinese herbal medicine Zengru Gao to promote breastfeeding: a multicenter randomized controlled trial

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Author’s response to reviews:

BCAM-D-16-01309

Efficacy of Chinese herbal medicine Zengru Gao to promote breastfeeding: a multicenter randomized controlled trial

Dear Professor Luis Vitetta,

I am pleased to resubmit the revised version of BCAM-D-16-01309 “Efficacy of Chinese herbal medicine Zengru Gao to promote breastfeeding: a multicenter randomized controlled trial” I appreciated the constructive criticisms of the editor and the reviewers. I have addressed each of their concerns as outlined below.
Sincerely yours,

Aiping Lu MD, PhD

Chair Professor

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Reviewer reports:

Alessandra Bazzano (Reviewer 1): The authors have undertaken important task of investigating the efficacy of the specified herb. However, English language editing is urgently required to improve the ability of the reader to understand the work completed. Additional details are also required in the Methods section and in the Discussion section to further clarify the work that was completed.

The constructive comments/suggestions by the reviewer is really appreciated. We have revised the whole manuscript carefully and tried to avoid any grammar or syntax error. In addition, we have asked two colleagues who are skilled authors of English language papers to check the English. We believe that the language is now acceptable for the review process. The Methods section and the Discussion section has rewritten as per reviewer’s suggestion and revised to clarify the details. Thank again for her kind comments.

Angela Lupattelli (Reviewer 2): Thank you for giving me the opportunity to review this manuscript. This is a randomized trial investigating whether the herbal remedy Zengru Gao was effective in promoting breastfeeding. The study is interesting, however there are some points that should be addressed by the authors. I recommend a proper English language editing of the entire manuscript; several English words are not appropriately used, and parts of the text are difficult to understand.

I received and read (& re-read) the appraisal. Overall the comments have been fair, encouraging and constructive. We have done thorough English editing and corrected the grammatical mistakes in the revised manuscript. We have carefully proofread the manuscript and edit it as following.
Introduction:

Please consider adding some prevalence estimates about breastfeeding practices and length of breastfeeding in the Chinese population.

Recent references have been incorporated in the revised manuscript.

Page 1, lines 16-17: the authors cite a study on herbal galactagogues, and it would help to describe what herbs were mainly used for this purpose in that study.

Page 1? Introduction section, we were attempting to inform the reader about the usage of herbal galactagogues, especially Zengru Gao. Many traditional Chinese herbs have been used to improve lactation potential. Semen Vaccariae is the seed of Vaccaria segetalis, known as Wang Bu Liu Xing in Chinese medicine, an annual herb widely distributed in Asia and other parts of the world. Medulla Tetrapanacisare, also known as Rice paper plant or Tong Cao in mandarin, is also a traditionally used Chinese medicinal plant. Semen Vaccariae and Medulla Tetrapanacis have been used widely to promote milk secretion [17, 18]. Main ingredients of Zengru Gao are Semen Vaccariae and Medulla Tetrapanacisare.

In the aim the authors state that the study was conducted among "first time mothers", however this information is not reflected in the Methods as well as in the Results (cf. figures on parity in Table 1). Could you please clarify?

Correction has been made in the revised manuscript.

Methods:

Please consider adding some information about the recruitment centers; it seems that all were public hospitals, however are the areas where the hospital are located comparable in terms of socioeconomic status of the inhabitants, or are there great differences? This information seems essential since the authors are not reporting any results stratified by center, or even the number of women recruited in each center.

As per reviewer request, we added a sentence to clarify the number of women recruited in each center. Two reasons why we decided to choose public hospitals. First, most women in China have their babies in public hospitals. Public maternity care in China is an affordable option that offers most birth choices. In public hospitals, most of the cost of mothers’ care is covered by China's basic medical insurance system. Second, China trial settings should be qualified to practice medicine and meet the qualifications specified by China food and drug administration requirement (http://app1.sfda.gov.cn/datasearch/face3/base.jsp?tableId=19&tableName=TABLE19&title=%)
all six settings in our study are qualified & experienced centers. To avoid the observations from the same center are more similar than those from different centers, clinical research standard operating procedures were made to help research department stay in compliance with good clinical practices.

Is "Blank group" the correct terminology?

It is a group that does not receive that intervention (control group). We have revised this phrase for clarity.

It is unclear to me how these women were approached for their potential inclusion in the study. Please clarify whether all women giving birth were asked to participate, how many women were asked, and thereby the response rate.

All women who had given birth at six hospitals were invited to participate. Women under 20 years or more than 35 years of age, or who were not contactable by telephone after discharge were not eligible for the study. Of the 898 women invited, 660 accepted the invitation, giving a response rate of 73.5%.

The description of the outcome measure is not extensive, and needs to be elaborated/clarified. It is unclear to me how the outcomes under study were ascertained; specifically, were the breastfeeding practices reported by the mothers?

We have added a detailed explanation in the methods pointing out the definition of the outcome measure. Actually, an accurate definition of breastfeeding was complex [1].


Could the authors clarify the rationale/utility of the outcome defined as "partially breastfeeding"? Beyond, I feel this wording is not really appropriate.

About "partially breastfeeding", we were referred to some high-quality research and analysis. Some of the references are as follows [1-3]:


My concern is that the authors are mainly measuring breastfeeding as a yes or no outcome, with no information about breast milk volume for instance. Since Zengru Gao is supposed to increase milk production, I feel this would be by far more important.

Method section, we have added quantitative outcome measure. Secondary outcomes were the volume of Baby’s daily formula intake and the frequency of adverse events in each group.

Also, it should be specified for how long these women and their breastfeeding practices were followed-up. In the Results section the authors described results at Day 7, however how useful would this follow-up time be?

Follow-up was performed at day 1, 3, 7 in hospitals or by telephone call at day 7 (when some women discharge from hospital) to record any subjective and objective change in feeding and any complications.

The paper does not contain any information about pharmacological properties of the herbal remedies under study; for instance, what is the induction time after oral administration of Zengru Gao for exerting its galactagogue effect?

In background section, we added applicable references to introduce pharmacological properties of herbs, includes Semen Vaccariae and Medulla Tetrapanacisare, the main ingredients of Zengru Gao.

The authors should clarify how long were these women hospitalized after delivery; if the follow-up time was 7 days, then it is expected that in some of these days women were at home, and no longer hospitalized. If this was the case, how did the research team control factors such as diet, drinking habits, used of medicines (both conventional and herbal)?
Women were received most of their protocol-specific education from the research team. After discharge from the hospitals, mothers were asked to record any adverse events that they experienced, diet, drinking habits, used of medicines as free text on the data sheet.

Another important note concerns the lack of any safety information about the breastfed children. Do the Zengru Gao components enter the breast milk, and if yes, what is the expected milk/plasma ratio? This aspect is not even addressed in the Discussion. I feel the Discussion lacks important reflections, especially on same of the points raised above.

That's very important. As an alternative to pharmaceutical agents, many clinicians recommend the use of herbs to improve milk output [1]. In a Norwegian study, it is estimated that 43% of breastfeeding women use herbal galactogogues [2], in a Chinese study, this estimate is 87.8% [3]. The herbs of Zengru Gao have been used for thousands of years. However, there is limited evidence explaining the mechanism of action of herbs as galactogogues, especially the milk to plasma concentration ratio of herbal remedy. More research and clinical trials are required in this area to guide the recommendations and expand our current knowledge of these products.


David M. Haas (Reviewer 3): Review for manuscript BCAM-D-16-01309

In this manuscript the authors report results of an RCT of an herbal supplement given postpartum to increase the milk production and breastfeeding of women in a multicenter Chinese RCT. This interesting study demonstrated that only at day 3 was there an improvement in breastfeeding and at dy 7 there was less formula used in the supplement group. I have a few questions/concerns for the authors.

We are thankful to Reviewer 3 for the encouraging and positive comments to improve the manuscript. We have considered the various suggestions made by the reviewer and have accordingly rewritten the manuscript.
1. Results from RCTS comparing proportions are more commonly reported as Relative Risks and confidence intervals, not a range of %s.

The percentage of fully and partially breastfeeding mothers among intervention group was compared with the percentages among control group to ascertain significant differences by chi-square tests.

2. Was this trial registered in a trial registry?

Certainly, registry number is ChiCTR-IPR-15007376. The details are published on China publicly-accessible website managed by a registry conforming to WHO standards.

3. Abstract conclusion states that the herbal drug was "well tolerance" Since these results are not presented in the abstract, it should not be in the abstract conclusion.

As per reviewer suggestion the phrase "well tolerance" has been removed.

4. It is apparent that there was no blinding of the participants or providers. this should be explicitly stated. However, were the outcomes assessors blinded as to the group assignment? Or did the people asking about breastfeeding outcomes also know if the woman was taking the supplement or nothing?

In the revised manuscript, we revised to clarify non-blinding method.

5. The rate of breastfeeding in both groups was higher than baseline hospital data stated in the sample size calculation. Were there any other programs going on in all or some of the hospitals to promote more breastfeeding. These might have been hiring of lactation consultants, removing free formula for moms, other interventions to promote breastfeeding. These could be confounders to the results.

All women were supported by the trained consultant nurse during the trial period and were educated similarly on proper breastfeeding techniques. Actually, to avoid research bias, there were no other programs going on to promote more breastfeeding during follow up. Day 3, percentage of fully and partially breastfeeding mothers in blank control group was 67.90%, slightly higher than prevalence value 65%.
6. Did the authors analyze results by site? Were there any differences in the individual sites in the results?

The points addressed by Reviewer 2 was taken into consideration and made necessary changes.

7. Breastfeeding was defined as direct from the breast. Were women excluded if they were pumping?

Yes, pumping style may influence milk production in mothers. Thus, women were excluded if they were pumping.

8. Figure 1 shows that 34 women were excluded for "other" reasons post randomization. This can introduce bias and these women should be accounted for and explained better why they were randomized.

Due to no response to phone calls n=22, pumping breast milk n=6, no longer breastfed due to cracked nipples n=6.

9. Results- the authors often state that rates were higher in the herbal group when there was not a statistically significant difference. This reveals a bias. Instead it should be stated that, "There was no clear difference between the groups in breastfeeding rates at day 1 or 7 or in the amount of formula supplementation on day 1 or 3."

The point was taken into consideration and made necessary changes.

10. Adverse events- The authors need to perform a statistical comparison of the rate of 5% complications/Adverse events to 0% in the control group. Also it is difficult to accept the final sentence in that section page 5 line 42 that says that no AEs were associated with the treatment when there were several that included infant effects and NONE in the control group.

Clinician's judgment suggested adverse experience was not associated with the use of Zengru Gao. The comparison of two groups was impossible because the investigators did not record any complication in blank control group. It is a major limitation of our study.
11. Discussion line 52 page 5 states that the supplement resulted in "a significant increase formula intake volumes..." This is incorrect as the data in text and Table 2 show decreased formula consumption.

Correction has been made in the revised manuscript.

12. Conclusion page 6 is confusing. The authors state that the results do not support the use of the herbal supplement but then states that the "obvious benefit" needs to be considered. Without breast milk data on the supplement and infant outcome data longer than 7 days, safety cannot be assumed.

As suggested, we have rewritten the conclusion. The conclusion is consistent with the result of 7 days follow up.

13. Table 1- the Pregnancy before number and Giving birth before number should likely be changed to gravidity and parity for consistency with other literature.

The authors thank Reviewer 3 for the suggestion. As per reviewer suggestion Table 1 has been revised.