

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chinese herbal medicine for postpartum constipation: a protocol of systematic review and meta-analysis
AUTHORS	Zhai, Jingbo; Li, Yan; Lin, Jingyi; Dong, Shuo; Si, Jinhua; Zhang, Junhua

VERSION 1 – REVIEW

REVIEWER	Bian zhao xiang Chinese medical college of Hong Kong Baptist University
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	<p>General comments</p> <p>This protocol will investigate the effectiveness and safety of Chinese herbal medicine for postpartum constipation, which is useful for clinical practice as the current evidence of conventional interventions for postpartum constipation is insufficient. This protocol is well designed, with comprehensive search, clear definition of outcomes and reasonable plan. It would be improved by focusing on the following suggestions and comments.</p> <p>Specific suggestions</p> <p>Page 2 line 28. The difference between postpartum constipation and constipation in adult should be stated clearly, are the therapies should be different in clinical practice. If they got a similar way for their treatment, then why should we treat them as two diseases.</p> <p>Page 3 line 27. The authors referred a Cochrane review of interventions for postpartum constipation, and said no RCTs were included, which I think it is not true, the review had been updated in 2015 and included five RCTs actually.</p> <p>Methods</p> <p>Page 3 line 51. The abbreviations should be used at the first place when you used them, you mentioned RTCs in the inductions, here it is not the first time mentioned, please change that and check other abbreviations.</p> <p>Page 3 line 51. If you have included RCTs, then the non RCTs, cross-over trials and so forth, are definitely excluded, then it is not necessary to state that.</p>
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	<p>Page 4 line 13. Bristol stool form scale was not used for diagnosis of constipation? the authors did not include this method in the diagnostic criteria.</p> <p>Page 4 line 44. Spontaneous bowel movement (SBM) was the only one primary outcome defined in this study, but in some other studies, such as the Cochrane review the authors mentioned in the introduction section, they also included pain or straining on defecation, Incidence of postpartum constipation and some other outcomes as primary outcomes. are there some special reasons for that in this study?</p> <p>Page 5 line 15. Why the Wanfang data is not included in searching sources? As we know that quite a lot high quality of Chinese journals from Chinese medical association, only included in Wangfang database since 1998.</p> <p>Page 5 line 24. I think it would be better to include the detailed search strategies about other databases in appendix 1, not just PubMed.</p> <p>Page 6 line 28. The reference number 30 should be updated, the Cochrane handbook have updated in 2017 [Chandler J, Higgins JPT, Deeks JJ, Davenport C, Clarke MJ. Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated February 2017), Cochrane, 2017. Available from Cochrane Community.]</p>
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REVIEWER	Raffaele Capasso University of Naples Federico II
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	<p>The paper is interesting.</p> <p>I have some question regarding this paper:</p> <p>I suggest the author to add in the introduction Rome III criterion regarding the constipations see review article by Cirillo and Capasso. Constipation and Botanical Medicines: An Overview. Phytother Res. 2015 Oct;29(10):1488-93.</p>
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REVIEWER	Robert Gaspar Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Szeged, Hungary
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	<p>The protocol of Zhai et al. is about the preparation of a systematic review for the therapeutic use of Chinese herbal medicine in case of postpartum constipation. The authors plan to review all the scientific papers that have been published about this issue since 1900. They do not want to restrict the search by any way. Although the postpartum constipation is a relevant clinical problem I feel that this proposal has several weaknesses:</p> <ol style="list-style-type: none"> 1. The search without restriction is risky, because if they find any paper in any language even from the beginning of the previous century, the justification of the correctness of data will be more the questionable. 2. I have made a quick search in PubMed with the key words "postpartum, constipation, herbal" or "postpartum, constipation, Chinese medicine", and only few (max. 5) paper has been found. I think it is a sign, that the reliable amount of studies in this topic is
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	<p>very low.</p> <p>3. Based on point 2, I cannot see real chance to find relevant data that helps to understand the differences in herbal therapy for constipation caused by different reasons during the postpartum period.</p> <p>4. The authors have not considered a major risk in their protocol: how the herbal medicine can influence the mother's milk production and how the herbal drugs reduce the possibility of healthy lactation that is essential for new-borns and infants.</p>
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REVIEWER	Mohammed S. Ali-Shtayeh Biodiversity and Environmental Research Center (BERC) Palestine
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	Use scientific writing all throughout the manuscript.
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REVIEWER	Dr Victoria Allgar University of York, England
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	I am not sure of the guidelines from the journal but as this is simply the protocol for the systematic review and presents no findings, I am not sure of the relevance. It is clearly written with appropriate proposed methodology but would be more interesting to see the findings.
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REVIEWER	Feng Yibin The University of Hong Kong
REVIEW RETURNED	16-Oct-2018

GENERAL COMMENTS	<p>This protocol aims to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of CHM for postpartum constipation. It should be of great interest to readers and important for enhancing quality of life of postpartum women. However, a few specific issues the authors should address by making modifications to the protocol or by clarifying in their response, after which I would consider this protocol suitable for publication in BMJ open.</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. Introduction: authors mentioned "quite a few clinical trials found CHM could have a role to play in the management of postpartum constipation", here meant only quite a few clinical trials had been conducted or quite a lot of clinical trials had been performed but only quite a few clinical trials found CHM could have a role? 2. Types of studies: if a study described it was a randomized controlled trial without reporting randomization method, will the study be considered as randomized controlled trial and included in the review? 3. Types of participants: please introduce the diagnostic criteria of constipation. 4. Multiple primary outcomes are used in the review. Authors should either define the most important issue as primary outcome or give the reasons why many primary outcomes have been chosen in the review. 5. Assessment of risk of bias in included studies: please define the criteria for unclear risk of bias. 6. Data synthesis: "We will perform the meta-analysis.....were similar across eligible studies." Please explain what the "similar"
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	<p>indicate here.</p> <p>7. Please discuss the implication and possible limitations of the study in the protocol.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Bian zhao xiang

Institution and Country: Chinese medical college of Hong Kong Baptist University

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

General comments

This protocol will investigate the effectiveness and safety of Chinese herbal medicine for postpartum constipation, which is useful for clinical practice as the current evidence of conventional interventions for postpartum constipation is insufficient. This protocol is well designed, with comprehensive search, clear definition of outcomes and reasonable plan. It would be improved by focusing on the following suggestions and comments.

Specific suggestions

Page 2 line 28. The difference between postpartum constipation and constipation in adult should be stated clearly, are the therapies should be different in clinical practice. If they got a similar way for their treatment, then why should we treat them as two diseases.

Response:

Thank you for your suggestions. The aetiology of postpartum constipation is multifactorial. Some factors account for both functional constipation in adults and postpartum constipation. Others are only associated with postpartum constipation. Now, no clinical recommendations have been provided for the management of postpartum constipation. Therefore, the choice of treatments for postpartum constipation remains a challenging clinical problem. We have made the advised changes on page 2.

Page 3 line 27. The authors referred a Cochrane review of interventions for postpartum constipation, and said no RCTs were included, which I think it is not true, the review had been updated in 2015 and included five RCTs actually.

Response:

Thank you for your suggestions. The 2015 Cochrane review evaluated the effectiveness and safety of interventions for preventing postpartum constipation. The 2014 cochrane review cited on page 3 focused on the effectiveness of interventions for treating postpartum constipation in which no RCTs were actually included. In this study, we focused on Chinese herbal medicine for treating postpartum constipation so that we have made no changes.

Methods

Page 3 line 51. The abbreviations should be used at the first place when you used them, you mentioned RTCs in the inductions, here it is not the first time mentioned, please change that and check other abbreviations.

Response:

Thank you for your suggestions. We have checked abbreviations and made the advised changes.

Page 3 line 51. If you have included RCTs, then the non RCTs, cross-over trials and so forth, are definitely excluded, then it is not necessary to state that.

Response:

Thank you for your suggestions. We have made the advised changes on page 3.

Page 4 line 13. Bristol stool form scale was not used for diagnosis of constipation? the authors did not include this method in the diagnostic criteria.

Response:

Thank you for your suggestions. We have made the advised changes in the section of 'Types of participants'.

Page 4 line 44. Spontaneous bowel movement (SBM) was the only one primary outcome defined in this study, but in some other studies, such as the Cochrane review the authors mentioned in the introduction section, they also included pain or straining on defecation, Incidence of postpartum constipation and some other outcomes as primary outcomes. are there some special reasons for that in this study?

Response:

Thank you for your suggestions. This study focuses on the treatment of postpartum constipation. Therefore, the incidence of postpartum constipation is not considered as the primary outcome. We know that more than one outcome is considered the primary outcome in some previous systematic reviews. When multiple outcome comparisons are included and review authors are free to choose and highlight single results among the many comparisons, there will be an increased risk of false declaration on the effectiveness of an assessed intervention (Jakobsen JC, Wetterslev J, Winkel P, et al. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014 Nov 21;14:120). Besides, SBM is selected as the primary outcome in many trials investigating the effectiveness of interventions for constipation. So SBM is considered as the only one primary outcome in this study. And some other indicators are considered as secondary outcomes.

Page 5 line 15. Why the Wanfang data is not included in searching sources? As we know that quite a lot high quality of Chinese journals from Chinese medical association, only included in Wangfang database since 1998.

Response:

Thank you for your suggestions. We have included Wanfang data in searching sources in the section of 'Electronic searches'.

Page 5 line 24. I think it would be better to include the detailed search strategies about other databases in appendix 1, not just PubMed.

Response:

Thank you for your suggestions. We have made the advised changes in appendix 1.

Page 6 line 28. The reference number 30 should be updated, the Cochrane handbook have updated in 2017 [Chandler J, Higgins JPT, Deeks JJ, Davenport C, Clarke MJ. Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated February 2017), Cochrane, 2017. Available from Cochrane Community.]

Response:

Thank you for your suggestions. We have made the advised changes in the section of references.

Reviewer: 2

Reviewer Name: Raffaele Capasso

Institution and Country: University of Naples Federico II

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

The paper is interesting.

I have some question regarding this paper:

I suggest the author to add in the introduction Rome III criterion regarding the constipations see review article by Cirillo and Capasso. Constipation and Botanical Medicines: An Overview. *Phytother Res.* 2015 Oct;29(10):1488-93.

Response:

Thank you for your suggestions. We have made the advised changes in the section of 'Types of participants'.

Reviewer: 3

Reviewer Name: Robert Gaspar

Institution and Country: Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Szeged, Hungary

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

The protocol of Zhai et al. is about the preparation of a systematic review for the therapeutic use of Chinese herbal medicine in case of postpartum constipation. The authors plan to review all the scientific papers that have been published about this issue since 1900. They do not want to restrict the search by any way.

Although the postpartum constipation is a relevant clinical problem I feel that this proposal has several weaknesses:

1. The search without restriction is risky, because if they find any paper in any language even from the beginning of the previous century, the justification of the correctness of data will be more the questionable.

Response:

Thank you for your suggestions. A systematic review attempts to collate all evidence that fits pre-specified eligibility criteria in order to answer a specific research question. Therefore, no language or publication date will be restricted. However, language and publication date may account for the between-study variability. So we will contact authors of included studies for providing further details or clarification whenever possible. Moreover, subgroup analyses will be used to explore possible sources of heterogeneity based on language or publication date. We have made the advised changes in the section of 'Subgroup analysis and investigation of heterogeneity'.

2. I have made a quick search in PubMed with the key words "postpartum, constipation, herbal" or "postpartum, constipation, Chinese medicine", and only few (max. 5) paper has been found. I think it is a sign, that the reliable amount of studies in this topic is very low.

Response:

Thank you for your suggestions. To our knowledge, many trials about Chinese herbal medicine for postpartum constipation have been indexed by Chinese medical databases but not by PubMed. A previous search in Chinese medical databases conducted by us showed that more than 10 reports met our inclusion criteria. In the future, the comprehensive search will be conducted to identify potentially other eligible studies. Therefore, we think that this study can provide valuable information for clinical practice.

3. Based on point 2, I cannot see real chance to find relevant data that helps to understand the differences in herbal therapy for constipation caused by different reasons during the postpartum period.

Response:

Thank you for your suggestions. Based on the response to point 2, we still have the chance to find relevant data that helps to understand the differences in herbal therapy for constipation caused by different reasons during the postpartum period. The subgroup analyses will be used to explore the differences based on the aetiology of postpartum constipation. We have made the advised changes in the section of 'Subgroup analysis and investigation of heterogeneity'.

4. The authors have not considered a major risk in their protocol: how the herbal medicine can influence the mother's milk production and how the herbal drugs reduce the possibility of healthy lactation that is essential for new-borns and infants.

Response:

Thank you for your suggestions. We will try to extract any adverse event of the intervention on both the mother and baby (such as influence of milk production, milk rejection, et al.) and estimate the incidence if possible. We have made the advised changes in the section of 'Types of outcome measures'.

Reviewer: 4

Reviewer Name: Mohammed S. Ali-Shtayeh

Institution and Country: Biodiversity and Environmental Research Center (BERC), Palestine

Please state any competing interests or state 'None declared': no competing interest

Please leave your comments for the authors below

Use scientific writing all throughout the manuscript.

Response:

Thank you for your suggestions. The manuscript has been professionally reviewed and edited by a native English speaker with expertise in my field in order to meet the standard of the scientific writing throughout the manuscript.

Reviewer: 5

Reviewer Name: Dr Victoria Allgar

Institution and Country: University of York, England

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I am not sure of the guidelines from the journal but as this is simply the protocol for the systematic review and presents no findings, I am not sure of the relevance. It is clearly written with appropriate proposed methodology but would be more interesting to see the findings.

Response:

Thanks for this useful comment. This protocol is written strictly according to the guideline from BMJ OPEN journal. We are also interesting to see the findings. We will perform this systematic review according to the current protocol and discuss these topics in the final systematic review report.

Reviewer: 6

Reviewer Name: Feng Yibin

Institution and Country: The University of Hong Kong

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This protocol aims to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of CHM for postpartum constipation. It should be of great interest to readers and important for enhancing quality of life of postpartum women. However, a few specific issues the authors should address by making modifications to the protocol or by clarifying in their response, after which I would consider this protocol suitable for publication in BMJ open.

Comments:

1. Introduction: authors mentioned "quite a few clinical trials found CHM could have a role to play in the management of postpartum constipation", here meant only quite a few clinical trials had been conducted or quite a lot of clinical trials had been performed but only quite a few clinical trials found CHM could have a role?

Response:

Thanks for this useful comment. The information may be described inaccurately. Many clinical trials found that CHM was beneficial for the management of postpartum constipation. We have made the advised changes in the section of 'Introduction'.

2. Types of studies: if a study described it was a randomized controlled trial without reporting randomization method, will the study be considered as randomized controlled trial and included in the review?

Response:

Thank you for your suggestions. If a study described that it was a randomized controlled trial without reporting randomization method, we will contact authors for providing further details or clarification whenever possible. If the information about the sequence generation process is insufficient to permit judgment of 'Low risk' or 'High risk', this study will still be included in this systematic review and the risk of selection bias will be graded as 'unclear'. We have made the advised changes in the section of 'Assessment of risk of bias in included studies'.

3. Types of participants: please introduce the diagnostic criteria of constipation.

Response:

Thank you for your suggestions. We have made the advised changes in the section of 'Types of participants'.

4. Multiple primary outcomes are used in the review. Authors should either define the most important issue as primary outcome or give the reasons why many primary outcomes have been chosen in the review.

Response:

Thank you for your suggestions. In this study, spontaneous bowel movement (SBM) is considered as the primary outcome. SBM can be measured by multiple methods, such as the incidence and frequency of SBM. Therefore, we will consider the incidence and frequency of SBM in 24 hour or per week, the mean number or the change of SBM per week from baseline in this study.

5. Assessment of risk of bias in included studies: please define the criteria for unclear risk of bias.

Response:

Thank you for your suggestions. We will assess the 'risk of bias' of included studies using the Cochrane Collaboration's tool for assessing risk of bias. This tool has clearly defined the criteria for 'low, high and unclear risk of bias'. We provided the related reference so that the specific judgment items for 'unclear risk of bias' were not listed.

6. Data synthesis: "We will perform the meta-analysis.....were similar across eligible studies." Please explain what the "similar" indicate here.

Response:

Thank you for your suggestions. The similarity means that more than one trial examines the same intervention and outcomes with comparable methods in similar populations. We have made the advised changes in the section of 'Data synthesis'.

7. Please discuss the implication and possible limitations of the study in the protocol.

Response:

Thank you for your suggestions. This systematic review will provide a comprehensive review of the efficacy and safety of Chinese herbal medicine for postpartum constipation. The evidence from this review may benefit patients with postpartum constipation and clinicians. It will also contribute to the development of relevant clinical guidelines. However, a large degree of heterogeneity in terms of methodological quality and outcome measures will likely pose challenges for study comparisons. We have made the advised changes in the section of 'Discussion'.

VERSION 2 – REVIEW

REVIEWER	Bian zhaoxiang Hong Kong Baptist University
REVIEW RETURNED	16-Nov-2018
GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.