

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

#### Title (Provisional)

Effect of acupoint hot compress on relieving pain in primiparous women during the latent phase of the first stage of labor: A study protocol for a prospective, multi-center, randomized controlled clinical trial

#### Authors

Li, Xinyue; Pu, Yuqun; Li, Nan; Zhou, Tianyi; Leng, Youjing; Zhu, Yuhang; Xu, Dong; Wang, Fangfang; Qu, Fan

### VERSION 1 - REVIEW

<b>Reviewer</b>	<b>1</b>
<b>Name</b>	<b>Fouly, Howieda</b>
<b>Affiliation</b>	<b>King Saud bin Abdulaziz University for Health Sciences</b>
<b>Date</b>	<b>12-Jan-2025</b>
<b>COI</b>	<b>None</b>

Dear/ Editor

Thank you so much for your invitation to review the manuscript “ Effect of acupoint hot compress on relieving pain in primiparous women during the latent phase of the first stage of labor: A study protocol for a prospective, multi center, randomized controlled clinical trial”

The manuscript is well-structured but can benefit from additional details to address missing parts, particularly related to ethical considerations, recruitment processes, justification of criteria, and management of data and risks.

Kindly find the comments below:

- The article topic is one of the interesting & important topic in the pain relive methods during childbirth pain.

Abstract:

The abstract written in the future tense using “ will” which need to be corrected to past tense as it is already conducted. Language editing is needed.

- Methods part missing setting, duration of study, and participants,

- Results & conclusions are missing from the abstract.

Strengths and limitations of this study: The language need editing to appropriate tense.

Methods: All the sections need language editing

The text offers a detailed description but there are several missing information, and clarification. The objective mentions evaluating pain relief and perinatal outcomes but does not specify the precise perinatal outcomes to be assessed (e.g., Apgar scores, maternal complications, neonatal weight) to clarify the focus.

There is no research question or hypothesis including in the study to be answered via study results.

Design of the Trial: more information is needed on the specific aspects (e.g., stopping rules, interim analyses, or ethical considerations) could be included.

Recruitment of Participants: Provide information about the recruitment process, inclusion timeline, and strategies for reaching the participants.

Exclusion Criteria: There is no rationale provided for excluding participants based on psychiatric disorders or sensory abnormalities.

Subject Withdrawal: The criteria detail for study withdrawal is missing.

Calculation of Sample Size: Provide details about the pilot study's sample size and its representativeness of the main study sample size.

Randomization and Blinding

Blinding: The author states "No blinding method used," but the rationale is missing.

Interventions

Control group: The description of obstetrical care is general and could be expanded for clarity.

Primary Outcome: Specify strategies to minimize confounding factors.

Secondary Outcomes: Incomplete details such as Blood loss measurement the author needs to specify how "quantitative measurements of the blood volume and weight" were performed. Explain the timing of EPDS administration (e.g., exactly at 48 hours or within a range) and define personnel responsible for scoring and whether they are blinded.

Data collection and management is missing elements of monitoring committees for data analysis is provided.

The study lacks a clear timeline for recruitment, intervention, follow-up, and analysis.

Discussion

The section lacks smooth transitions between paragraphs, for example:

- The phrase, "The World Health Organization (WHO) describes..." introduces a new topic abruptly without tying it to the preceding methodology.
- The part about "hot compress" and "gate control theory" feels disjointed, with sentences appearing out of sequence (e.g., "According to the gate control theory, the hot compress..." and the mention of blood vessel dilation are split).

The limitations section identifies several issues but lacks clarity and depth: the author needs rephrase and elaborate on how each limitation could influence outcomes.

General comment: The manuscript has to ensure logical flow with clear transitions between methodology, results, and implications. Justify statistical methods and provide details on the intervention. Address ethical considerations and broader implications of the study. Refine the limitations section to acknowledge their impact and propose mitigation strategies and editing for grammatical and typographical errors for clarity and professionalism.

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<b>Reviewer</b>	<b>2</b>
<b>Name</b>	<b>Amiri Farahani, Leila</b>
<b>Affiliation</b>	<b>Iran University of Medical Sciences</b>
<b>Date</b>	<b>06-Feb-2025</b>
<b>COI</b>	<b>None</b>

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Thank you for giving me the opportunity to review this article.

One of the issues that the authors need to explain is the latent phase. As a midwife, I know that the latent phase is very variable in individuals and it may take up to two to three weeks after the onset of individual contractions for them to enter the active phase, and it is not possible to say exactly when it started. That is, the start time of entering the latent phase is not clear based on midwifery books. If the authors have used an index to accurately measure the onset of the latent phase and the entry of people with similar characteristics in two studies, please refer to it in the abstract and in the text of the article. Does pain that is not very intense and the interval between pains is usually long need to be relieved?

The second issue was what was the necessity of writing the protocol article? It is true that the sample size of the study is large, but the duration of each woman's presence in the study was only for a few hours and based on the information provided in the abstract, the long-term outcome is not measured. What was the necessity of designing the protocol?

What is meant by regular contractions in the method? What index was used to measure it?

In the conclusion of the abstract, perinatal outcomes are mentioned, while in the method, there is no information about how to measure it and the items measured.

Statement of the problem

Most of the material mentioned in the statement of the problem is a reference to articles that were about pain in the first and second stages of labor, that is, in the active phase of labor. I still have a question about intervention in the latent phase. Does this stage require intervention? A stage where pain is usually limited, slight, infrequent, and of low intensity.

It is necessary to refer to those studies if interventions have been performed in the latent phase and to rewrite the study accordingly.

In the general objective of the study and in the title of the study, it is necessary to mention that the intervention was performed in the latent phase and to make it the same everywhere. Both in the abstract and in the text of the article.

## Method

Inclusion criteria with the study should be written on one line, not in bullet points.

What was the indicator that was used to define the latent phase based on reference 17?

It is better to categorize the criteria for selecting participants under the headings of inclusion criteria, exclusion criteria, and withdrawal criteria.

Given that the latent phase is not the phase of voluntary hospitalization for childbirth. Specify where and by whom the intervention will be performed on the participant?

In the method, it is necessary to provide explanations about the validity and reliability of the instruments used to measure the primary and secondary outcomes.

## Discussion

In the discussion, it is necessary to provide explanations about the application of the findings.

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## VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Howieda Fouly, King Saud bin Abdulaziz University for Health Sciences

Comments to the Author:

Dear/ Editor

Thank you so much for your invitation to review the manuscript “ Effect of acupoint hot compress on relieving pain in primiparous women during the latent phase of the first stage of labor: A study protocol for a prospective, multi center, randomized controlled clinical trial”

The manuscript is well-structured but can benefit from additional details to address missing parts, particularly related to ethical considerations, recruitment processes, justification of criteria, and management of data and risks.

Kindly find the comments below:

- The article topic is one of the interesting & important topic in the pain relive methods during childbirth pain.

Abstract:

The abstract written in the future tense using “will” which need to be corrected to past tense as it is already conducted. Language editing is needed.

**Response:** Thank you for the comment! Since this manuscript is a study protocol, describing the planned design and methodology of a clinical trial that is currently ongoing, the future tense (“will”) is conventionally used to describe prospective interventions, outcomes, and analyses according to the SPIRIT guidelines for protocol reporting and common editorial standards [1]. We have retained this tense to maintain consistency with the nature of the article.

[1] Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207. doi:10.7326/0003-4819-158-3-201302050-00583

- Methods part missing setting, duration of study, and participants,

**Response:** Thank you for the comment! As suggested, in the methods part, we have added details on the study setting (18 institutions in China), duration (January 2024-August 2025) and participant eligibility criteria in the revised manuscript.

- Results & conclusions are missing from the abstract.

**Response:** Thank you for the comment! Since this is a protocol that is currently ongoing, the results and conclusions are not yet available.

Strengths and limitations of this study: The language need editing to appropriate tense.

**Response:** Thank you for the comment! As suggested, we have revised the Strengths and limitations section. However, we have retained the future tense due to the nature of the protocol.

Methods: All the sections need language editing

The text offers a detailed description but there are several missing information, and clarification. The objective mentions evaluating pain relief and perinatal outcomes but does not specify the precise perinatal outcomes to be assessed (e.g., Apgar scores, maternal complications, neonatal weight) to clarify the focus.

**Response:** Thank you for the comment! As suggested, we have specified the precise perinatal outcomes, including labor duration, intrapartum and postpartum bleeding, maternal depression symptoms, and neonatal Apgar scores in the revised manuscript.

There is no research question or hypothesis including in the study to be answered via study results.

**Response:** Thank you for the comment! As suggested, we have added research hypothesis in the Hypothesis section to provide a clearer focus on the aim of study.

Design of the Trial: more information is needed on the specific aspects (e.g., stopping rules, interim analyses, or ethical considerations) could be included.

**Response:** Thank you for the comment! As suggested, we have added detailed information on stopping rules in the Design of the Trial section. For ethical considerations, we have described them in detail in the Ethics and Dissemination section to avoid redundancy. Since no interim analyses are planned for this study, we have not mentioned them.

Recruitment of Participants: Provide information about the recruitment process, inclusion timeline, and strategies for reaching the participants.

**Response:** Thank you for the comment! As suggested, in the Recruitment of participants section, we have added the information about the recruitment process, inclusion timeline, and strategies for reaching the participants in the revised manuscript.

Exclusion Criteria: There is no rationale provided for excluding participants based on psychiatric disorders or sensory abnormalities.

**Response:** Thank you for the comment! We appreciate the opportunity to clarify the reasons behind the exclusion criteria related to psychiatric disorders and sensory abnormalities. This is based on the following reasons: First, individuals with psychiatric disorders are excluded to minimize potential confounding effects on self-reported pain assessments [1-2] and to ensure the validity of depression symptom evaluations via EPDS scores. Second, individuals with sensory abnormalities are excluded to reduce potential risks of thermal injury from the hot compress intervention.

[1] Fishbain DA, Gao J, Lewis JE, Bruns D, Meyer LJ, Disorbio JM. Prevalence comparisons of somatic and psychiatric symptoms between community nonpatients without pain, acute pain patients, and chronic pain patients. *Pain Med.* 2015 Jan;16(1):37-50. doi: 10.1111/pme.12527.

[2] Antioch I, Ilie OD, Ciobica A, Doroftei B, Fornaro M. Preclinical Considerations about Affective Disorders and Pain: A Broadly Intertwined, yet Often Under-Explored, Relationship Having Major Clinical Implications. *Medicina (Kaunas).* 2020 Sep 25;56(10):504. doi: 10.3390/medicina56100504.

Subject Withdrawal: The criteria detail for study withdrawal is missing.

**Response:** Thank you for the comment! As suggested, we have added the detail in the Subject Withdrawal section in the revised manuscript.

Calculation of Sample Size: Provide details about the pilot study's sample size and its representativeness of the main study sample size.

**Response:** Thank you for the comment! As suggested, we have provided the details about the pilot study's sample size (n=50) and its representativeness of the main study sample size to the Calculation of Sample Size section in the revised manuscript.

### Randomization and Blinding

Blinding: The author states "No blinding method used," but the rationale is missing.

**Response:** Thank you for the comment! As suggested, we have added the rationale for not using the blinding method to the Randomization and Blinding section in the revised manuscript.

### Interventions

Control group: The description of obstetrical care is general and could be expanded for clarity.

**Response:** Thank you for the comment! As suggested, to enhance clarity while avoiding redundancy, we have revised the Interventions section by adding a direct reference to the control group's detailed obstetrical care (Section 2.11.1) within the intervention group description. Additionally, the intervention group description now explicitly emphasizes the sole addition of acupoint hot compress therapy, thereby highlighting the study's core focus.

Primary Outcome: Specify strategies to minimize confounding factors.

**Response:** Thank you for the comment! As suggested, we have added the detailed strategies to minimize confounding factors in the revised manuscript.

Secondary Outcomes: Incomplete details such as Blood loss measurement the author needs to specify how "quantitative measurements of the blood volume and weight" were performed.

**Response:** Thank you for the comment! As suggested, we have revised the manuscript to provide a more detailed description of the blood loss measurement methodology.



Explain the timing of EPDS administration (e.g., exactly at 48 hours or within a range) and define personnel responsible for scoring and whether they are blinded.

**Response:** Thank you for the comment! As suggested, we have clarified that the EPDS will be administered within 48 hours postpartum. Since the EPDS is a self-reported tool completed by participants, blinding of personnel is not applicable. Trained researchers will collect and record the questionnaires to ensure data consistency.

Data collection and management is missing elements of monitoring committees for data analysis is provided.

**Response:** Thank you for the comment! Although our institution does not have a formal Data and Safety Monitoring Board (DSMB), we have implemented comprehensive measures to ensure data integrity and ethical oversight. As suggested, we added the details in the revised manuscript.

The study lacks a clear timeline for recruitment, intervention, follow-up, and analysis.

**Response:** Thank you for your comment. Please allow us to clarify that, as this is a study protocol, the research is currently ongoing, and the final clear timeline will depend on recruitment and intervention progress. Although a detailed, fixed timeline is not yet available, we have indeed provided a timeline in Supplementary material 1 of our protocol. This table outlines the projected phases and provides a structured view of our study.

## Discussion

The section lacks smooth transitions between paragraphs, for example:

- The phrase, "The World Health Organization (WHO) describes..." introduces a new topic abruptly without tying it to the preceding methodology.

**Response:** Thank you for the comment! As suggested, we have revised the Discussion section to improve paragraph transitions.

- The part about "hot compress" and "gate control theory" feels disjointed, with sentences appearing out of sequence (e.g., "According to the gate control theory, the hot compress..." and the mention of blood vessel dilation are split).

**Response:** Thank you for the comment! As suggested, we have revised the Discussion section to improve the flow and coherence.

The limitations section identifies several issues but lacks clarity and depth: the author needs rephrase and elaborate on how each limitation could influence outcomes.

**Response:** Thank you for the comment! As suggested, we have revised the Limitations section to provide a clearer and more detailed discussion of how each limitation could influence the study outcomes.

General comment: The manuscript has to ensure logical flow with clear transitions between methodology, results, and implications. Justify statistical methods and provide details on the intervention. Address ethical considerations and broader implications of the study. Refine the limitations section to acknowledge their impact and propose mitigation strategies and editing for grammatical and typographical errors for clarity and professionalism.

**Response:** Thank you for your thorough and constructive feedback on our manuscript. We sincerely appreciate the time and effort you dedicated to evaluating our work. As suggested, we have carefully revised the corresponding part in the revised manuscript.

Your insights have significantly improved the quality of this work. Thank you once again for your invaluable guidance.

Reviewer: 2

Dr. Leila Amiri Farahani, Iran University of Medical Sciences

Comments to the Author:

Thank you for giving me the opportunity to review this article.

One of the issues that the authors need to explain is the latent phase. As a midwife, I know that the latent phase is very variable in individuals and it may take up to two to three weeks after the onset of individual contractions for them to enter the active phase, and it is not possible to say exactly when it started. That is, the start time of entering the latent phase is not clear based on midwifery books. If the authors have used an index to accurately measure the onset of the latent phase and the entry of people with similar characteristics in two studies, please refer to it in the abstract and in the text of the article.

**Response:** Thank you for your insightful comments regarding the latent phase of labor. We fully acknowledge that the onset of the latent phase can indeed be unclear, as noted in midwifery books. In the existing literature, regular painful contractions are the most common indicators for the onset of latent phase labor [1]. In our study, the acupoint hot compress therapy will be applied starting one hour after the onset of regular uterine contractions, and this approach ensures that the intervention is delivered during the latent phase.

[1] Hanley GE, Munro S, Greyson D, Gross MM, Hundley V, Spiby H, Janssen PA. Diagnosing onset of labor: a systematic review of definitions in the research literature. *BMC Pregnancy Childbirth*. 2016 Apr 2;16:71. doi: 10.1186/s12884-016-0857-4.

Does pain that is not very intense and the interval between pains is usually long need to be relieved?

**Response:** Thank you for the comment! On the matter of pain relief during the latent phase, we understand that the intensity and interval of pains can be highly subjective and vary greatly among individuals. While some women may experience mild discomfort that does not necessitate intervention, others may find the pain intolerable and request pain relief [1]. Therefore, we emphasize that the decision to administer pain relief should be made on a case-by-case basis, taking into account the woman's individual preferences, pain tolerance, and the potential risks and benefits of the available interventions.

[1] Mueller AN, Grylka-Baeschlin S. Self-management, care needs and clinical management of primiparous mothers during early labour - a qualitative content analysis. *BMC Pregnancy Childbirth*. 2023 Mar 18;23(1):191. doi: 10.1186/s12884-023-05453-4.

The second issue was what was the necessity of writing the protocol article? It is true that the sample size of the study is large, but the duration of each woman's presence in the study was only for a few hours and based on the information provided in the abstract, the long-term outcome is not measured. What was the necessity of designing the protocol?

**Response:** Thank you for the comment! We fully understand your concern. As suggested, we have added the lack of long-term outcomes in the limitations section of the discussion. Although long-term outcomes are not measured in this study, the primary focus is on evaluating the immediate effects of acupoint hot compress on labor pain which are critical for informing clinical practice. Additionally, while the duration of each participant's involvement in the study is only a few hours, failure to promptly address pain during the latent phase of labor can have lasting psychological effects, as prolonged pain and anxiety during this phase may contribute to negative childbirth experiences and reduced maternal satisfaction [1]. Moreover, the necessity of designing the protocol also lies in its multi-center design, involving 18 clinical centers across China. This large-scale collaboration necessitates the implementation of standardized protocols to ensure consistency in intervention delivery, data collection, and



outcome assessment.

[1] Sutton E, Detering K, East C, Whittaker A. Women's expectations about birth, requests for pain relief in labor and the subsequent development of birth dissonance and trauma. *BMC Pregnancy Childbirth*. 2023 Nov 9;23(1):777. doi: 10.1186/s12884-023-06066-7.

What is meant by regular contractions in the method? What index was used to measure it?

**Response:** Thank you for the comment! In our study, regular contractions refer to uterine contractions that occur at a consistent frequency (every 5-6 minutes) and duration (lasting at least 30 seconds) [1]. We adopt a combination of clinical assessments to measure and confirm the presence of regular contractions. These include periodic palpation by midwives or obstetricians to evaluate the regularity, intensity, and pattern of the contractions. Additionally, cervical examinations are conducted to further validate the contractions by evaluating cervical dilation and effacement.

[1] Chinese Maternal and Child Health Association Midwives Branch, Chinese Maternal and Child Health Association Committee for Promoting Natural Childbirth. Clinical practice guideline of normal birth. *Chinese Journal of Obstetrics and Gynecology*. 2020 Jun 25;55(6):371-375. DOI: 10.3760/cma.j.cn112141-20200428-00363. (In Chinese)

In the conclusion of the abstract, perinatal outcomes are mentioned, while in the method, there is no information about how to measure it and the items measured.

**Response:** Thank you for the comment! Given that this article is a protocol and the study is still ongoing, we have removed the conclusion section to comply with the journal's guidelines. Additionally, to enhance clarity, we have revised the "perinatal outcomes" in the abstract and objectives to "key maternal and neonatal outcomes", specifying these as labor duration, intrapartum and postpartum bleeding, maternal depression symptoms, and neonatal Apgar scores.

Statement of the problem

Most of the material mentioned in the statement of the problem is a reference to articles that were about pain in the first and second stages of labor, that is, in the active phase of labor. I still have a question about intervention in the latent phase. Does this stage require intervention? A stage where pain is usually limited, slight, infrequent, and of low intensity.

**Response:** Thank you for the comment! We acknowledge that pain during the latent phase is typically less intense compared to the active phase. However, it is important to note that pain perception varies significantly among individuals, and some women may experience intense pain even during the latent phase. As highlighted in ACOG Committee Opinion No. 766, when women are observed or admitted for pain in latent labor, non-pharmacologic pain management techniques may be beneficial [1]. Many women express a desire for pain relief options throughout labor, including the early stages, to alleviate discomfort and reduce anxiety. If not addressed promptly, such pain can lead to prolonged psychological stress, increased anxiety, and a negative childbirth experience [2]. By offering a non-invasive intervention during the latent phase, we aim to provide a more holistic and patient-centered approach to labor care, aligning with current recommendations and addressing the diverse needs of women during childbirth.

[1] ACOG Committee Opinion No. 766: Approaches to Limit Intervention During Labor and Birth. *Obstet Gynecol*. 2019 Feb;133(2):e164-e173. doi: 10.1097/AOG.0000000000003074.

[2] Sutton E, Detering K, East C, Whittaker A. Women's expectations about birth, requests for pain relief in labor and the subsequent development of birth dissonance and trauma. *BMC Pregnancy Childbirth*. 2023 Nov 9;23(1):777. doi: 10.1186/s12884-023-06066-7.

It is necessary to refer to those studies if interventions have been performed in the latent phase and to rewrite the study accordingly.

**Response:** Thank you for the comment! As suggested, we have revised the manuscript to include relevant studies that access non-pharmacological interventions during the latent phase.

In the general objective of the study and in the title of the study, it is necessary to mention that the intervention was performed in the latent phase and to make it the same everywhere. Both in the abstract and in the text of the article.

**Response:** Thank you for the comment! As suggested, we have revised the manuscript to explicitly mention that the intervention will be performed during the latent phase of the first stage of labor.

## Method

Inclusion criteria with the study should be written on one line, not in bullet points.

**Response:** Thank you for the comment! As suggested, we have written the inclusion criteria on one line in the revised manuscript.

What was the indicator that was used to define the latent phase based on reference 17?

**Response:** Thank you for your comment! Based on the WHO recommendations: Intrapartum care for a positive childbirth experience (reference 17 in original manuscript), the latent phase is defined as the period from the onset of regular uterine contractions to cervical dilation of less than 5 cm. This definition is also adopted by the Clinical Practice Guideline of Normal Birth in China (2020) [1]. However, we fully acknowledge that the definition of the latent phase remains highly controversial, and no universal consensus has been reached [2-3]. In our study, we followed the criteria outlined in WHO recommendations to define the latent phase, ensuring consistency with current clinical standards in China.

[1] Chinese Maternal and Child Health Association Midwives Branch, Chinese Maternal and Child Health Association Committee for Promoting Natural Childbirth. Clinical practice guideline of normal birth. Chinese Journal of Obstetrics and Gynecology. 2020 Jun 25;55(6):371-375. DOI: 10.3760/cma.j.cn112141-20200428-00363. (In Chinese)

[2] ACOG Committee Opinion No. 766: Approaches to Limit Intervention During Labor and Birth. Obstet Gynecol. 2019 Feb;133(2):e164-e173. doi: 10.1097/AOG.0000000000003074.

[3] National Institute for Health and Care Excellence. Intrapartum Care for Healthy Women and Babies, Guideline CG190. London: National Institute for Health and Care Excellence, 2014.

It is better to categorize the criteria for selecting participants under the headings of inclusion criteria, exclusion criteria, and withdrawal criteria.

**Response:** Thank you for the comment! As suggested, we have revised the manuscript to categorize the criteria for selecting participants under the headings of Inclusion Criteria, Exclusion Criteria, and Withdrawal Criteria for better clarity and readability.

Given that the latent phase is not the phase of voluntary hospitalization for childbirth. Specify where and by whom the intervention will be performed on the participant?

**Response:** Thank you for the comment! In China, it is generally observed that pregnant women are admitted to the hospital during the early stages of labor, often before the onset of regular uterine contractions (i.e., during irregular contractions or the very early latent phase). This practice is influenced by cultural preferences and the healthcare system's emphasis on close monitoring during childbirth [1]. As a result, participants in our study will already be

hospitalized before the intervention is initiated. Specifically, the acupoint hot compress intervention will be performed in the hospital setting by trained professionals, including obstetricians, midwives and nurses who have received standardized training in the application of acupoint hot compress techniques. These professionals will closely monitor the participants to ensure that the intervention is administered safely and effectively.

[1] Liu X, Yan H, Wang D. The evaluation of "Safe Motherhood" program on maternal care utilization in rural western China: a difference in difference approach. BMC Public Health. 2010 Sep 22;10:566. doi: 10.1186/1471-2458-10-566.

In the method, it is necessary to provide explanations about the validity and reliability of the instruments used to measure the primary and secondary outcomes.

**Response:** Thank you for the comment! As suggested, we have provided validity and reliability data for VAS, EPDS, and Apgar scores, supported by cited literature.

#### Discussion

In the discussion, it is necessary to provide explanations about the application of the findings.

**Response:** Thank you for the comment! As suggested, we have revised the Discussion section to include a detailed explanation of the potential applications of our findings.