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)

Median nerve electrical stimulation for restoring consciousness in patients with traumatic brain injury: study protocol for a systematic review and meta-analysis

Authors

Yang, Ying; Luo, Yulan; Feng, Mei; Luo, Ping; Zeng, Jiarong; Shi, Xinmao; Tang, Menglin

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Bertolini, Gladson Ricardo Flor**
Affiliation	**Universidade Estadual do Oeste do Paraná**
Date	**26-Aug-2024**
COI	**none.**

The manuscript is a protocol for a systematic review with meta-analysis. I think the authors should include the protocol in some database, such as Prospero or OSF.

Reviewer	**2**
Name	**Kumaria, Ashwin**
Affiliation	**Queen's Medical Centre, Department of Neurosurgery**
Date	**05-Sep-2024**
COI	**None**

Thank you for this opportunity to review.

This article outlines the protocol for a systematic review and meta-analysis for median nerve stimulation in disorders of consciousness after traumatic brain injury.

The protocol and search strategy are thorough. There are no concerns with the methodology as proposed.

The manuscript is written well and I have no particular concerns.

Reviewer	**3**
Name	**Zhu, Luwen**
Affiliation Affiliated Hospital	**Heilongjiang University of Chinese Medicine, Fourth**
Date	**08-Sep-2024**
COI	**No**

This article presents an innovative protocol for a systematic review and meta-analysis, aiming to assess the efficacy and safety of median nerve electrical stimulation (MNES) in the recovery of disorders of consciousness (DOC) among patients with traumatic brain injury (TBI), based on a recently published high-quality randomized controlled trial (RCT). However, there are several key issues in the study design that require further refinement and optimization.

1. In the methods section, the intervention group includes various MNES stimulation techniques, while the control group only receives conventional treatment. This design may introduce variables and heterogeneity, making it difficult to isolate the effect of MNES alone. In a rigorous RCT, both the intervention and control groups should be as consistent as possible to avoid confounding factors.

2. MNES stimulation should be a specific and well-defined protocol for median nerve electrical stimulation. Including both electroacupuncture and transcutaneous stimulation creates confusion, as these methods differ in their mechanisms and effects. A review of the literature shows that MNES typically refers to a single electrical stimulation technique and does not encompass multiple methods like electroacupuncture, which introduces unnecessary variability.

3. In the subgroup analysis, the protocol plans to stratify by the severity of TBI, gender, age, and comorbidities. However, since multiple stimulation methods are included in the intervention group, this will introduce additional heterogeneity. Furthermore, the frequency, intensity, and duration of the median nerve stimulation could also be sources of heterogeneity.

Ref:

(1) Wu X, Xie L, Lei J, Yao J, Li J, Ruan L, Hong J, Zheng G, Cheng Y, Long L, Wang J, Huang C, Xie Q, Zhang X, He J, Yu X, Lv S, Sun Z, Liu D, Li X, Zhu J, Yang X, Wang D, Bao Y, Maas AIR, Menon D, Xue Y, Jiang J, Feng J, Gao G; ACES Participants. Acute traumatic coma awakening by right median nerve electrical stimulation: a randomised controlled trial. Intensive Care Med. 2023 Jun;49(6):633-644.

(2) Cooper JB, Jane JA, Alves WM, Cooper EB. Right median nerve electrical stimulation to hasten awakening from coma. Brain Inj. 1999 Apr;13(4):261-7.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1:

1. The manuscript is a protocol for a systematic review with meta-analysis. I think the authors should include the protocol in some database, such as Prospero or OSF.

Response: Thank you for your valuable comments and instructions. We have registered the protocol in the Prospero database and ensured that the content in the database is updated in a timely.

Reviewer 2:

1. This article outlines the protocol for a systematic review and meta-analysis for median nerve stimulation in disorders of consciousness after traumatic brain injury. The protocol and search strategy are thorough. There are no concerns with the methodology as proposed. The manuscript is written well and I have no particular concerns.

Response: We appreciate your recognition of our protocol and manuscript. We are committed to further enhancing the quality of our work through continuous efforts and improvement.

Reviewer 3:

1. In the methods section, the intervention group includes various MNES stimulation techniques, while the control group only receives conventional treatment. This design may introduce variables and heterogeneity, making it difficult to isolate the effect of MNES alone. In a rigorous RCT, both the intervention and control groups should be as consistent as possible to avoid confounding factors.

Response: Thank you for your valuable comments and instructions. We discussed the intervention techniques included in the study, and it was found that incorporating electroacupuncture and transcutaneous acupoint electrical stimulation therapy would indeed bring significant confounding factors. Therefore, we modified the types of intervention measures to only include MNES stimulation techniques.

2. MNES stimulation should be a specific and well-defined protocol for median nerve electrical stimulation. Including both electroacupuncture and transcutaneous stimulation creates confusion, as these methods differ in their mechanisms and effects. A review of the literature shows that MNES typically refers to a single electrical stimulation technique and does not encompass multiple methods like electroacupuncture, which introduces unnecessary variability.

Response: Thank you for your valuable comments and instructions. To avoid unnecessary variability introduced by other electrical stimulation techniques such as electroacupuncture. We have modified the types of intervention measures.

Corresponding revision has been made in the section Methods as follows:

The intervention of interest in this study only includes MNES therapy. However,

it does not include other forms of stimulation that place electrodes on the right side of the median nerve or both palmar sides, such as electroacupuncture and transcutaneous acupoint electrical stimulation. The specific parameters of the MNES intervention will be no restrictions, including the stimulation intensity, frequency, duration, or treatment cycle. The control group will be patients receiving conventional treatment or sham MNES.

3. In the subgroup analysis, the protocol plans to stratify by the severity of TBI, gender, age, and comorbidities. However, since multiple stimulation methods are included in the intervention group, this will introduce additional heterogeneity. Furthermore, the frequency, intensity, and duration of the median nerve stimulation could also be sources of heterogeneity.

Response: Thank you for your valuable comments and instructions. We have revised the inclusion of the intervention group to only include MNES therapy. Based on your suggestion, we will also include the frequency, intensity, duration, and treatment cycle of MNES in the subgroup analysis.

Corresponding revision has been made in the section Methods as follows:

If the sensitivity analysis fails to adequately explain the observed heterogeneity, we will conduct subgroup analyses to explore the potential sources of variability. The subgroup analyses will be based on the following study-level characteristics: severity of traumatic brain injury, gender of participants, age of participants, presence of comorbidities, frequency, intensity, duration, and treatment cycle of MNES.

VERSION 2 - REVIEW

Reviewer	**3**
Name	**Zhu, Luwen**
Affiliation	**Heilongjiang University of Chinese Medicine, Fourth Affiliated Hospital**
Date	**16-Oct-2024**
COI	

The author has revised the manuscript in response to comments.