

The effectiveness of non-invasive brain stimulation on arousal and alertness in patients in coma or persistent vegetative state after traumatic brain injury

Protocol of systematic review and network meta-analysis

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Abstract

Background: Traumatic brain injury is a leading cause of death and disability worldwide. The survivors usually suffer from disorders of consciousness, especially coma state and persistent vegetative state. For these patients, there is no standard treatment for them, but non-invasive brain stimulations are considered as relatively more acceptable treatments. However, the knowledge regarding the relative effectiveness and the rank of the effectiveness of the non-invasive brain stimulations is limited. Thus, in this study, we aim to conduct a systematic review and network meta-analysis to evaluate the effect of non-invasive brain stimulations on arousal and alertness in patients in a coma or persistent vegetative state after traumatic brain injury.

Methods and analysis: A comprehensive search strategy will be performed in the relevant databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Wan Fang Data). The random or quasi-random controlled trials focusing on the effectiveness of the non-invasive brain stimulations will be included. The risk of bias for the included studies will be appraised using the Cochrane collaboration tool for assessing risk of bias. The standard pairwise meta-analysis and a Bayesian network meta-analysis will be conducted.

Ethics and dissemination: This research is a systematic review and network meta-analysis. Thus, there is no requirement of ethical approval and patient informed consent.

PROSPERO registration number: CRD42018104945.

Abbreviations: CI = confidence interval, DIC = deviance information criteria, DOC = disorders of consciousness, DRS = Disability Rating Scale, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GRADE = Grading of Recommendation, Assessment, Development, and Evaluation, ICTRP = International Clinical Trials Registry Platform, LCF = level of cognitive functioning, MCS = minimally conscious state, MDs = mean differences, NMA = network meta-analysis, ORs = odd ratios, PRISMA-P = preferred reporting items for systematic review and meta-analysis protocol, PVS = persistent vegetative state, RMNS = right median nerve stimulation, SS = sensory stimulation, TBI = traumatic brain injury, TDCS = transcranial direct current stimulation, TMS = transcranial magnetic stimulation, UWS = unresponsive wakefulness syndrome, VR = virtual reality, WHO = World Health Organization.

Keywords: coma state, network meta-analysis, non-invasive brain stimulation, persistent vegetative state, systematic review, traumatic brain injury

The authors declare no conflicts of interest.

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1. Background

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide, particularly in Southeast Asian and Western Pacific regions.^[1] In each year, about 5.48 million people (73 cases per 100,000) suffer from severe TBI,^[1] of which most survivors get disorders of consciousness (DOC). Majority of these patients turn into a coma state, and generally the coma survivors may enter a gradual recovery process of consciousness^[2]—firstly into unresponsive wakefulness syndrome (UWS) which is also called persistent vegetative state (PVS) if the patient has kept in a vegetative state for more than 4 weeks, then into a minimally conscious state (MCS) until getting out from DOC. But around 10%^[3,4] to 30%^[5] coma survivors remain in PVS even after about 1 month. Moreover, about 50% of patients who have been experienced PVS for at least 4 weeks after head injury

remain in this state 1 year post-TBI [3,4,6,7]; and approximately 23% of MCS patients don't recover their consciousness 1 year after TBI.^[8,9]

From the financial perspective, it brings great burden to the family and society. For example, a previous review showed that the costs per case were from about \$34,000 for mild to about \$60,000 for moderate TBI.^[10] Unfortunately, so much expense is spent, but there is no standard care which may result in cost-effectiveness for these patients.^[11] Even though several previous systematic reviews^[12–16] have systematically evaluated the potential effective treatments for these patients, the credible evidence has not been found because of a small number of relevant trails, the small sample size, inconsistency, old evidence grading system, and so on. Owing to the limited evidence on the effect of the interventions, the non-invasive brain stimulations (including right median nerve stimulation [RMNS], sensory stimulation [SS], transcranial magnetic stimulation [TMS], transcranial direct current stimulation [TDCS], and virtual reality [VR]), with little harm and adverse effect, are considered as relatively more acceptable treatments. In the recent years, more new relevant studies assessing the effectiveness of non-invasive brain stimulations have been published or are conducting.^[17–22] With the newly published studies and more patients participating in the researches, we are likely able to confirm the effectiveness of non-invasive brain stimulations. In addition, the existing systematic reviews only conducted the pairwise meta-analysis to compare the efficacy of different types of non-invasive brain stimulations by head-to-head. The knowledge regarding the rank of the effectiveness of the non-invasive brain stimulations is limited. To the best of our knowledge, network meta-analysis (NMA)^[23] is developed to address this problem, which is able to confirm the relative effectiveness among all the potential interventions and rank the order of the effect of interventions when head-to-head comparisons lack. Therefore, in this study, we aim to conduct a comprehensive systematic review and network meta-analysis to evaluate the effectiveness of the non-invasive brain stimulations on arousal and alertness in patients in coma or persistent vegetative state after traumatic brain injury.

2. Methods

We have registered the protocol of this systematic review and network meta-analysis on the PROSPERO international prospective register of systematic reviews (Register number: CRD42018104945). The reporting of this protocol was in accordant with the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P),^[24,25] and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions.^[26]

2.1. Eligibility criteria

We plan to include the studies which meet the following criteria: the patients in the coma or vegetative state after traumatic brain injury without limitation on the age; aim to evaluate the effectiveness of the non-invasive brain stimulations through the comparisons of: one of the non-invasive stimulations (including SS, TDCS, TMS, RMNS, and VR) versus each other or usual care; multi-stimulations versus uni-stimulation or usual care; different types of combination of multi-stimulations; report at least one of the following outcomes: the rate of awakening, duration of unconsciousness, level of consciousness measured by

the Glasgow Coma Scale (GCS), level of cognitive functioning (LCF), functional outcomes measured by Glasgow Outcome Scale (GOS) or Disability Rating Scale (DRS), adverse effects (ie, increased intracranial pressure); random or quasi-random controlled trials (during the study screening stage, the relevant systematic reviews, and meta-analyses will also be included for tracking their references).

2.2. Information source

A comprehensive search strategy will be developed, which will be mainly led by an author (DW) together with the group discussion. We will search the databases below: Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE (via PubMed), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, and Wan Fang Data. The ongoing studies and the studies which have been completed but not yet published will be searched through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/Default.aspx>).

We will check the references of included articles to retrieve further relevant studies.

2.3. Search strategy

The electronic search will be performed from the inception of databases to August 2018 and without any language limitation. We plan to use the search terms regarding the targeted participants together with the non-invasive sensory stimulations, which the details of the search strategy in PubMed can be seen below:

1. “Coma, Post-Head Injury” [Mesh] OR “Persistent Vegetative State” [Mesh] OR “Brain Injuries/complications” [Mesh] OR “vegetative state” [Title/Abstract] OR coma [Title/Abstract]
2. “Electric Stimulation” [Mesh] OR “Transcranial Direct Current Stimulation” [Mesh] OR “Transcranial Magnetic Stimulation” [Mesh] OR “Virtual Reality Exposure Therapy” [Mesh] OR “sensory stimulation” [Title/Abstract] OR “transcranial direct current stimulation” [Title/Abstract] OR “transcranial magnetic stimulation” [Title/Abstract] OR “right median nerve stimulation” [Title/Abstract] OR “virtual reality” [Title/Abstract] OR videogame [Title/Abstract] OR tdc [Title/Abstract] OR tms [Title/Abstract] OR rmns [Title/Abstract] OR vr [Title/Abstract]
3. 1 AND 2

More information on search strategy in the rest databases can be found in the supplement file, <http://links.lww.com/MD/C480>.

2.4. Study selection and data extraction

Firstly, the records retrieved from the databases will be imported to EndNote X7 literature management software by DW who is professional on searching the electronic databases and conducting a systematic review. Then, pairs of researchers will screen the records independently by reviewing the title and abstract. In the next step, the pairs of researchers will review the full-texts of the potential eligible studies independently.

With an electronic form, the following data will be extracted by pairs of researchers independently: study characteristics (such as title, first author, publication type, publication year, country, journal, the sponsor), study design (inclusion and exclusion criteria, generation of allocation sequence, allocation conceal-

ment and blinding, length of follow-up), participant data (sample size, race, age, diagnosis [condition] of the patients, diagnostic criteria, co-morbidities, lost/withdrawal), details of interventions of interest (type, protocol, frequency, duration), and outcomes (measured tools, time point, results).

Before study selection and data extraction, we plan to do a pilot test for each assignment respectively in order to ensure high inter-rater reliability among the researchers. When there are disagreements between a pair of researchers, discussion will be organized and the conflicts will be solved by a third researcher (DW).

2.5. Risk of bias assessment

The tool for assessing risk of bias developed by Cochrane collaboration^[27] will be applied to appraise the risk of bias of included randomized controlled trials (RCTs) by pairs of independent researchers. There are 7 domains in this tool, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain is evaluated as low, high, unclear risk of bias. The support for the adjustments will be recorded. Discussion will be organized and conflict will be solved by DW, when there are disagreements.

2.6. Data synthesis

2.6.1. Dealing with missing data. For the important data such as the standard deviations or standard errors of the continuous outcomes, if they were not reported in the articles, we will firstly calculate it by ourselves based on the reported information such as confidence interval (CI) or *P*-value. If the reported data is not enough for calculation, we plan to the authors to obtain the data. What's worse, if no data is not successfully got from the authors, the methods suggested by Furukawa et al^[28] will be used to retrieve the missing data. The assumptions derived from these data will be tested through sensitivity analysis.

2.6.2. Standard pairwise meta-analysis. We will pool odds ratios (ORs) and mean differences (MDs) with 95% CI for the dichotomous and continuous outcomes respectively by performing the pairwise meta-analysis in STATA V.12.0 (Stata Corporation, College Station, Texas). The effects model will be chosen after assessing the heterogeneity by I^2 statistics. If $I^2 \leq 50\%$, we will use the Mantel-Haenszel fixed effects model to pool the data. Otherwise, firstly subgroup analysis and meta-regression will be performed to test the sources of heterogeneity. If no evidence on clinical heterogeneity is found, the Mantel-Haenszel random effects model will be chosen. But if there is apparent clinical heterogeneity, we plan to do subgroup analysis (if available) or only describe the results of the included studies respectively. With regard to the assessment of reporting bias, the Begg and Egger funnel plot method will be used.^[29,30] And the contour-enhanced funnel plot will be used to help to distinguish asymmetry, if multi-factors lead to publication bias.^[31]

2.6.3. Network meta-analysis. Firstly, a network plot of the treatment network of comparisons across trials will be drawn to assess whether the network meta-analysis is available. In the network geometry, nodes and edges stand for the interventions and the head-to-head comparisons between them separately. The bigger the node is, the larger the sample size focused on the intervention is; and the thicker the edge is, the more trials focused on the comparison there are.

Next, we plan to conduct the Bayesian network meta-analysis by the code from Dias et al^[32] in WinBUGS 1.4.3. The pooled estimation and the rank of the effect of the interventions will be obtained according to the Markov Chains Monte Carlo method. We plan to run three Markov Chains simultaneously and firstly generate 50,000 simulations for each chain which these simulations will be discarded as the 'burn-in' period; 100,000 subsequent simulations will be chosen for the posterior summaries. We will evaluate the model convergence by trace plots and Brooks-Gelman-Rubin plots,^[33] and assess the statistical heterogeneity in the entire network according to the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from the network meta-analysis models using R-3.2.2 software. If a loop connecting three arms exists, inconsistency between direct and indirect comparisons will be evaluated using a node splitting method.^[34] The choices between fixed and random effect models, consistent and inconsistent models, will be made by comparing the deviance information criteria (DIC) for each model.^[32,35] The model with the lowest DIC will be preferred (differences >3 are considered significant).

With regard to the sources of heterogeneity or inconsistency in the entire network, the network meta-regression or subgroup analysis will be conducted. We will conduct the network meta-regression under the random effects models to assess the potential effect moderators such as follow-up and sample size.

If there are enough trials for comparison, we plan to conduct a sensitivity analysis by excluding trials which miss the relative data and the trials with a total sample size of <50 randomized patients.

2.7. Quality of evidence

We will use the Grading of Recommendation, Assessment, Development and Evaluation approach (GRADE) to assess the quality of evidence—how much confidence we have on the effect estimation.^[36] The process will be performed on the platform of GRADEpro – GDT (<https://gradepro.org/>).

2.8. Ethics and dissemination

This research is a systematic review and network meta-analysis. Thus, there is no requirement of ethical approval and patient informed consent.

3. Discussion

To our knowledge, this is the first network meta-analysis which compares the effectiveness of different non-invasive brain stimulations on arousal and alertness in patients in coma or persistent vegetative state after traumatic brain injury. The quality of evidence rated through GRADE approach in this review would clearly inform the evidence users the extent to which we believe that the findings are truth. Thus, the findings of this review would be likely to inform the decision making on healthcare for those patients in clinical practice.

Author contributions

Contributors: Conception and design of this systematic review and Bayesian network meta-analysis (Yabin Li, Xianggui Luo, Miao Wan, Dang Wei, Haixia Feng); tested the feasibility of the study (Yabin Li, Xianggui Luo, Miao Wan, Jiao Li, Hongxia Wang); developed the search strategy (Dang Wei, Miao Wan,

Xianggui Luo); drafted this protocol (Yabin Li, Xianggui Luo, Miao Wan, Haixia Feng), revised the protocol (Yabin Li, Xianggui Luo, Miao Wan, Jiao Li, Hongxia Wang, Dang Wei). All authors provided critical revisions of the protocol and approved the final article.

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