INPLASY PROTOCOL

To cite: Nunes et al. Non-invasive Brain Stimulation in the Management of COVID-19: Protocol for a Systematic Review. Inplasy protocol 2022120033. doi: 10.37766/inplasy2022.12.0033

Received: 08 December 2022

Published: 08 December 2022

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Support: **UFABC.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Non-invasive Brain Stimulation in the Management of COVID-19: Protocol for a Systematic Review

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Review question / Objective: **What is the efficacy or effectiveness of NIBS techniques, specifically repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcutaneous auricular vagus nerve stimulation (taVNS), percutaneous auricular vagus nerve stimulation (paVNS), and neck vagus nerve stimulation (nVNS), in the control of outcomes associated with COVID-19 in the acute or post-COVID persistent syndrome?**
Eligibility criteria: **Included clinical studies assessed participants with acute or persistent post-COVID-19 syndrome submitted to NIBS interventions, namely transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), theta burst (cTBS or iTBS). Studies that used peripheral and spinal cord stimulation techniques were also included. Those included vagus nerve stimulation (VNS), such as transcutaneous auricular (taVNS), percutaneous auricular (paVNS), transcranial random noise stimulation (tRNS) trans-spinal direct current stimulation (tsDCS) and other peripheral electrical stimulation (PES) techniques. Scientific communication, protocol studies, reviews and non-English papers were excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 December 2022 and was last updated on 08 December 2022 (registration number INPLASY2022120033).

INTRODUCTION

Review question / Objective: **What is the efficacy or effectiveness of NIBS techniques, specifically repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation**

(tDCS), transcranial alternating current stimulation (tACS), transcutaneous auricular vagus nerve stimulation (taVNS), percutaneous auricular vagus nerve stimulation (paVNS), and neck vagus nerve stimulation (nVNS), in the control of outcomes associated with COVID-19 in the acute or post-COVID persistent syndrome?

Rationale: The clinical use of non-invasive brain stimulation (NIBS) to treat COVID-19 patients has already been suggested after the initiation of the pandemic in December 2019. It has been hypothesized that NIBS may be used in the control of the cytokine storm related to the disease, as well as to manage the respiratory and psychiatric symptoms, pain, and fatigue by influencing autonomic functioning and other areas of the brain related to COVID-19 neurological, musculoskeletal and psychiatric dysfunctions, but the evidence about this use is scarce.

Condition being studied: Acute COVID-19 and Long-COVID-19.

METHODS

Search strategy: ((COVID-19) OR (SARS-CoV-2)) AND ((((((((((((((((((((((("noninvasive neuromodulation") OR ("non-invasive neuromodulation")) OR ("noninvasive brain stimulation")) OR ("non-invasive brain stimulation")) OR (NIBS)) OR ("transcranial direct current stimulation")) OR (tDCS)) OR ("transcranial magnetic stimulation")) OR (TMS)) OR ("repetitive transcranial magnetic stimulation")) OR (rTMS)) OR ("theta burst")) OR (cTBS)) OR (iTBS)) OR ("transcranial alternating current stimulation")) OR (tACS)) OR ("vagus nerve stimulation")) OR (VNS)) OR ("transauricular vagus nerve stimulation")) OR (taVNS)) OR ("transcranial random noise stimulation")) OR (tRNS)) OR ("peripheral electric stimulation")) OR (PES)) OR ("transpinal direct current stimulation")) OR (tsDCS)).

Participant or population: Participants with acute or persistent post-COVID-19 syndrome.

Intervention: Transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), theta burst (cTBS or iTBS). Studies that used peripheral and spinal cord stimulation techniques were also included. Those included vagus nerve stimulation (VNS), such as transcutaneous auricular (taVNS), percutaneous auricular (paVNS), transcranial random noise stimulation (tRNS) trans-spinal direct current stimulation (tsDCS) and other peripheral electrical stimulation (PES) techniques

Comparator: Sham or any other intervention.

Study designs to be included: Randomized clinical trials, open trials, case studies, case series.

Eligibility criteria: Included clinical studies assessed participants with acute or persistent post-COVID-19 syndrome submitted to NIBS interventions, namely transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS), theta burst (cTBS or iTBS). Studies that used peripheral and spinal cord stimulation techniques were also included. Those included vagus nerve stimulation (VNS), such as transcutaneous auricular (taVNS), percutaneous auricular (paVNS), transcranial random noise stimulation (tRNS) trans-spinal direct current stimulation (tsDCS) and other peripheral electrical stimulation (PES) techniques. Scientific communication, protocol studies, reviews and non-English papers were excluded.

Information sources: This is a systematic review of clinical studies of NIBS in COVID-19, registered in XXX and following the PRISMA 2020 guideline. Pubmed database has been searched using the strategy described in the next section.

Manual searches were also performed through websites, organizations, citation searches, and registries of clinical trials, from April 2020 to December 2022.

Main outcome(s): Emergency severity index at presentation; Blood pressure (systolic/diastolic); Time on supplemental oxygen; Spirometry (22); Incidence of non-invasive positive pressure ventilation or heated high flow nasal cannula use; Days on non-invasive positive pressure ventilation or heated high-flow nasal cannula use; Occurrence of ICU transfer from non-ICU hospital bed and time to transfer; Duration of ICU stay in days; Occurrence of mechanical ventilation; Days to and on mechanical ventilation; Time to clinical recovery, respiratory rate, oxygen saturation, and alleviation of cough, sustained for at least 72 hours. Normalization and alleviation criteria are as follows: Fever - ≤36.6°C or -axilla, ≤37.2 °C oral or ≤37.8°C rectal or tympanic; Respiratory rate - ≤24/minute on room air; Oxygen saturation - >94% on room air; Cough - mild or absent on a patient-reported scale of severe, moderate, mild, or absent; Hospital length of stay (LOS); All-cause mortality; Fatigue; Pain; Assessment of chemical senses (olfactory and gustatory). Outpatient studies: Body temperature, twice daily (morning and evening); Ambulatory spirometry (Mo et al.) – or, at least, breathing measures (training spirometry may be tough); Headache ; Respiratory rate – may or may not be elevated; Fatigue; Pain; Assessment of chemical senses (olfactory and gustatory); Neurological symptoms.

Additional outcome(s): No additional outcomes.

Data management: Selection process - Two independent reviewers (AFB and IN) researched the literature. In case of disagreement regarding the selection of a study, a third reviewer (KNS) was consulted. Data collection process
Each reviewer searched the literature for articles on the subject on a weekly basis, including or excluding them based on the title and abstract. Selected articles were read in search of results that can be extracted to assess the effectiveness of non-invasive neuromodulation in controlling COVID-19 symptoms.
The following data categories were extracted: Author, year of publication, study design, sample size, clinical outcomes, type of stimulation, parameters of non-invasive neuromodulation, and main results. In cases of missing data, the respective authors were contacted. Papers with insufficient data were excluded from the analysis. Data extraction and management were done using the web app Rayyan (for screening and duplication).

Quality assessment / Risk of bias analysis: Study risk of bias assessment - We analyzed the Risk of Bias through Rob-2 Scale to assess the randomized clinical trials considering selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Two authors (APG and MR) did the first analysis and a third (KNS) was asked to do the tiebreak.

Strategy of data synthesis: Study risk of bias assessment - We analyzed the Risk of Bias through Rob-2 Scale to assess the randomized clinical trials considering selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Two authors (APG and MR) did the first analysis and a third (KNS) was asked to do the tiebreak.
Certainly assessment - We planned to assess the certainty of evidence through the GRADE-pro system. However, due to the reduced number of published clinical trials, it was not possible to determine the level of evidence.

Subgroup analysis: No subgroup analysis is planned.

Sensitivity analysis: We analyzed the Risk of Bias through Rob-2 Scale to assess the randomized clinical trials considering selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Two authors (APG and MR)

did the first analysis and a third (KNS) was asked to do the tiebreak.

Language restriction: we included only English-written texts.

Country(ies) involved: Brazil.

Other relevant information: No other relevant information.

Keywords: Transcranial Direct Current Stimulation, Transcranial Magnetic Stimulation, Vagus Nerve Stimulation, Coronavirus Infection.

Dissemination plans: After finishing this study we plan to submit it as a pre-print to SRRN and then submit the final text to Brain Stimulation.

Contributions of each author:

Author 1 - Isadora Nunes - Design of the study, data collection and analysis, and writing the final version of the manuscript.
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