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

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

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Abstract

Introduction

Traumatic brain injury (TBI) is one of the prevalent critical illnesses encountered in clinical practice, with survivors often experiencing varying degrees of consciousness disorders. Long-term consciousness disorders can increase the risk of complications, such as urinary tract infections and pulmonary infections, leading to poor prognosis and significantly impacting patients' quality of life. Clinical studies have reported that median nerve electrical stimulation

(MNES) may have a therapeutic effect in the treatment of disorders of consciousness (DOC). We plan to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of MNES in the management of DOC following TBI.

Methods and analysis

We will conduct a comprehensive literature search in the following electronic databases: Web of Science, Embase, PubMed, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), and Chinese Scientific Journal Database (VIP). The search will be performed from the inception of the databases until June 30, 2024. Additionally, we will search for relevant ongoing trials in the International Clinical Trial Registry Platform (ICTRP), ClinicalTrials.gov, and China Clinical Trial Registry (Chi-CRT). We will also identify "grey literature" from GreyNet International, Open Grey, and Google Scholar. We will include eligible randomized controlled trials (RCTs). The primary outcome of interest will be the assessment of consciousness disorder severity. Two independent reviewers will screen the studies for inclusion, extract relevant data, and assess the risk of bias. Any discrepancies will be resolved through discussion or consultation with a third reviewer. The quality of evidence will be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Data synthesis and meta-analysis will be conducted using STATA 15.1 software.

Ethics and dissemination

This systematic review and meta-analysis does not involve the collection or use of any individual patient data; therefore, no ethical review is required. The research findings will be disseminated through publication in peer-reviewed scientific journals.

Strengths and limitations of this study

This will be the first comprehensive systematic review and meta-analysis to evaluate the effects of MNES on the improvement of DOC following TBI.

The independent dual-reviewer process for study selection and data extraction, with the involvement of a third reviewer to resolve any disagreements, enhances the reliability and accuracy of the review.

The use of Egger's and Begg's tests, along with the trim and fill method, helps to evaluate and address the potential impact of publication bias.

The included studies may vary significantly in terms of their methodological approaches, patient populations, and details of the median nerve electrical stimulation protocols, which could introduce substantial heterogeneity and limit the ability to pool and interpret the results.

The generalizability of the review's conclusions may be constrained by factors such as variations in healthcare systems, cultural contexts, and resource availability across different settings.

Systematic review registration

This systematic review and meta-analysis has been prospectively registered on the PROSPERO, with the registration number CRD42024533359.

Keywords:

Median nerve electrical stimulation, Traumatic brain injury, Disorders of consciousness, Systematic review and meta-analysis.

Introduction

Traumatic brain injury (TBI) is a brain injury caused by external mechanical forces, which can lead to permanent or temporary impairment of cognitive, physical, and psychological functions. Notably, TBI is often accompanied by alterations in consciousness, and it represents a significant cause of mortality and disability[1-2]. Every year, 69 million people worldwide suffer from TBI[3], with a mortality rate of 20% -30%[4]. Furthermore, it is projected to remain the leading cause of neurological disability by 2031[5], posing a significant public health burden globally. In recent years, advancements in emergency medicine and intensive care technologies have led to improved survival rates for TBI patients[6]. However, many individuals who sustain severe TBI may experience disorders of consciousness (DOC), including coma, vegetative state (VS)/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS)[7]. Long-term consciousness disorders not only impose a heavy economic burden but also place significant mental and emotional strain on the patients' families and society as a whole[8].

DOC following TBI is associated with widespread functional changes caused by focal brain injury or more comprehensive neural damage[79]. This includes injury to the brainstem reticular ascending activation system (ARAS), disruption of neurotransmitters that maintain the sleep-wake cycle, and diffuse lesions in the cerebral cortex. After injury to the ARAS, which is responsible for regulating the human sleep-wake cycle, patients may remain in a prolonged sleep state[10]. Research has shown that up to 14% of TBI patients experience long-term coma or persistent VS, and the longer the coma duration, the higher the mortality rate[11-12].The incidence of medical complications in patients with prolonged DOC is high[13], including

muscle tone hyperactivity, sleep disorders, urinary tract infections, hydrocephalus, and pneumonia. These complications can negatively impact the rehabilitation process, quality of life, and mortality rate[14-15]. Shortening the duration of DOC may help improve outcomes and increase patient participation in rehabilitation therapy[16]. Therefore, finding ways to shorten the awakening process and reduce the risk of long-term disability in TBI patients with DOC has become a crucial issue in the field of neurological rehabilitation research.

Current treatment approaches for promoting the recovery of DOC following TBI include pharmacological interventions, such as amantadine and zolpidem[17-18], as well as invasive brain stimulation therapies, including vagus nerve stimulation and deep brain stimulation[19-20]. However, the existing evidence is insufficient to support the sustained or long-term improvement effects of these treatment modalities. Additionally, the adverse reactions associated with medications and invasive procedures, such as the increased risk of infection and disease deterioration[21-22], limit their clinical application, relegating them to mainly adjunctive roles. In recent years, the exploration of non-invasive stimulation technologies to facilitate awakening has emerged as a research focus in this field. As a non-invasive physical therapy method, MNES has been widely utilized for various nerve-related conditions due to its demonstrated therapeutic benefits[23-24]. Some clinical trials have also reported that MNES may be a potential intervention to accelerate the recovery from DOC following TBI[25-26]. MNES places electrodes on the median nerve for electrical stimulation, exerting central excitatory effects, reactivating suppressed neurons and the ARAS, increasing blood perfusion and brain-derived neurotrophic factor, ultimately promoting awakening[27-28].

However, a systematic evaluation of the clinical evidence regarding the efficacy and safety of MNES in the management of DOC following TBI is currently lacking. This systematic

review and meta-analysis aims to provide a comprehensive, evidence-based assessment of the potential benefits and risks of MNES as an intervention for awakening in TBI patients.

Methods

This study will be conducted in strict accordance with the *Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines.*[29-30]

Inclusion criteria

Types of studies

This study will only include randomized controlled trials (RCTs), without any language or regional restrictions. We will exclude non-clinical research types, such as cohort studies, purely theoretical studies, case reports, editorials, commentaries, or expert opinions.

Types of participants

The population of interest for this systematic review will be adult patients (aged 18 years and above, with no gender restrictions) who have been diagnosed with DOC following closed TBI. Patients will be excluded if they have any of the following conditions: unstable vital signs, history of epilepsy, pregnancy, severe arrhythmias, or the presence of a pacemaker.

Types of interventions and comparisons

The intervention of interest in this study is MNES therapy. This includes various stimulation methods, such as neuromuscular electrical stimulation, electroacupuncture, and percutaneous acupoint electrical stimulation, where electrodes are placed at the right or bilateral palmar positions of the median nerve. The specific parameters of the MNES intervention will be no

restrictions, including the stimulation intensity, frequency, duration, or course of treatment. The comparator group will be patients receiving conventional treatment, which may include rehabilitation therapy, nutritional support, and medication management.

Types of outcomes

Primary outcomes

The proportion of patients who regained consciousness after 6 months.

Secondary outcomes

1. Clinical Behavior Checklist for Evaluating Consciousness Disorders

Glasgow Coma Scale (GCS), Coma Recovery Scale-Revised (CRS-R), Wessex Head Injury Matrix (WHIM), and Full Outline of UnResponsiveness (FOUR).

2. Disability Rating Scale (DRS)

3. Incidence of complications

4. Electrophysiological and neuroimaging evaluation.

5. Incidence of adverse events (AEs).

Information sources

Electronic databases

We will conduct a comprehensive literature search in the following electronic databases: Web of Science, Embase, PubMed, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), and Chinese Scientific Journal Database (VIP). The search will be performed from the inception of the databases until June 30, 2024. Additionally, we will manually search the reference lists of the retrieved articles to identify any potentially eligible studies. There will be no restrictions on language or

publication status.

Other resources

In addition to the electronic database searches, we will conduct a comprehensive search of clinical trial registration platforms to identify any ongoing or unpublished trials relevant to our review. These platforms will include the World Health Organization's International Clinical Trial Registration Platform, ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and the Cochrane Central Register of Controlled Trials. Furthermore, we will search for valuable grey literature through specialized websites, such as GreyNet International, OpenGrey, and Google Scholar. This approach will help us identify any additional relevant studies that may not have been published in the peer-reviewed literature, thereby reducing the risk of publication bias and enhancing the completeness of our systematic review.

Search strategy

To ensure the rigor and accuracy of the literature search, we will develop a comprehensive search strategy based on the PICOS framework. This will involve the use of both subject-specific keywords and free-text terms to capture all relevant studies. As an example, the detailed search strategy for the PubMed database is presented in **Table 1**.

Table 1 Search strategy for PubMed

Sequence	Items
#1	Brain Injuries, Traumatic (MeSH)
#2	Traumatic Brain Injuries
#3	Trauma, Brain
#4	Brain Trauma
#5	Brain Traumas
#6	Traumas, Brain
#7	Traumatic Brain Injury
#8	Encephalopathy, Traumatic

#9	Encephalopathies, Traumatic
#10	Traumatic Encephalopathies
#11	Injury, Brain, Traumatic
#12	Traumatic Encephalopathy
#13	TBI
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	Coma (MeSH)
#16	Comas
#17	Comatose
#18	Consciousness Disorders (MeSH)
#19	Consciousness Disorder
#20	Disorder of Consciousness
#21	Disorders of Consciousness
#22	Consciousness, Level Depressed
#23	Depressed Level of Consciousness
#24	Consciousness, Level Altered
#25	Altered Level of Consciousness
#26	Semiconsciousness
#27	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	Electric Stimulation Therapy (MeSH)
#29	Therapy, Electric Stimulation
#30	Stimulation Therapy, Electric
#31	Electrotherapy
#32	Therapeutic Electric Stimulation
#33	Electric Stimulation, Therapeutic
#34	Stimulation, Therapeutic Electric
#35	Electrical Stimulation Therapy
#36	Stimulation Therapy, Electrical
#37	Therapy, Electrical Stimulation
#38	Therapeutic Electrical Stimulation
#39	Electrical Stimulation, Therapeutic
#40	Stimulation, Therapeutic Electrical
#41	Interferential Current Electrotherapy
#42	Electrotherapy, Interferential Current
#43	Transcutaneous Electric Nerve Stimulation
#44	Electroacupuncture
#45	Median nerve electrical stimulation
#46	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47	Clinical trials (MeSH)

#48	Randomized Clinical trials
#49	Randomized
#50	Random
#51	Placebo
#52	Trial
#53	Groups
#54	#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#55	#14 AND #27 AND #46 AND #54

Selection of studies

Two independent researchers will first screen the titles and abstracts of the retrieved literature to exclude any studies that are not relevant to this review. They will then thoroughly review the full-text articles to assess eligibility based on the predefined inclusion and exclusion criteria. Any disagreements will be discussed and resolved with the third researcher.

The selection process is shown in Figure 1.

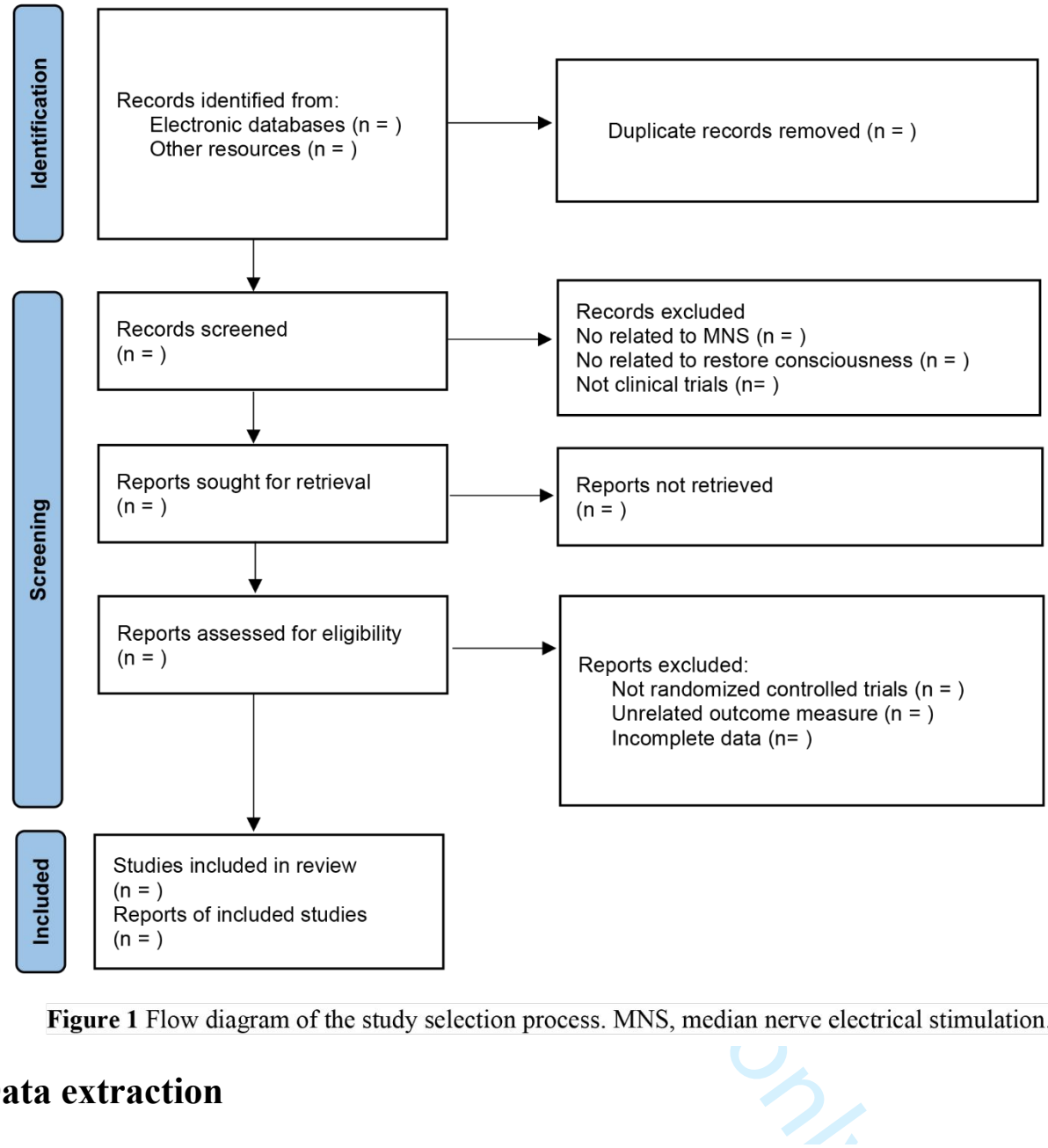

Figure 1 Flow diagram of the study selection process. MNS, median nerve electrical stimulation.

Data extraction

Two independent research teams will extract data from the included studies using a pre-designed data extraction table. The information to be collected will include the first author, publication year, nationality, sample size of experimental and control groups, participant characteristics (age, gender, comorbidities, etc.), details of the intervention (stimulation parameters, treatment duration, and course), outcome measures (consciousness assessment scales, disability rating scales, reported adverse events, etc.). The data extraction process will

be conducted independently by the two research teams. Any discrepancies or disagreements that arise during this process will be resolved through discussion and consultation with a third researcher if necessary.

Risk of bias assessment

The risk of bias assessment for the included studies will be conducted based on the Cochrane Systematic Review Manual (version 5.1.0). The following key domains will be evaluated: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, completeness of outcome data, selective reporting, and other potential sources of bias. Each domain will be judged as having a low risk of bias, an unclear risk of bias, or a high risk of bias, according to the predefined criteria outlined in the Cochrane Handbook. Any disagreements will be discussed and resolved with the third researcher.

Data synthesis

The data analysis will be conducted using Stata version 15.0. For continuous data, we will use the standardized mean difference (SMD) and 95% confidence intervals (95%CI) to quantify the effect sizes. For dichotomous data, we will calculate the odds ratio (OR) and 95% CI to estimate the treatment effects. Statistical significance will be determined based on whether the 95% CI of the SMD does not include 0 or the 95% CI of the OR does not include 1. If the 95% CI does not encompass these values, the difference will be considered statistically significant.

Assessment of heterogeneity

The assessment of heterogeneity will be conducted using the I^2 statistic. If the $I^2 < 50\%$ with the $P > 0.1$, the heterogeneity across the included studies will be considered low. In such cases, a fixed-effects model will be used to perform the meta-analysis calculations. However, if the $I^2 > 50\%$ or $P \leq 0.1$, significant heterogeneity will be present. In this scenario, sensitivity

analyses and subgroup analyses will be performed to explore the potential sources of heterogeneity. If the subgroup analyses are unable to adequately address the observed heterogeneity, a random-effects model will be used for the meta-analysis calculations.

Sensitivity analysis

To assess the robustness of the meta-analysis results, we will conduct a sensitivity analysis by sequentially removing each study from the analysis and re-estimating the overall effect size.

Subgroup analysis

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, and presence of comorbidities.

Assessment of publication bias

To assess the potential presence of publication bias, we will conduct Egger's linear regression test and Begg's rank correlation test. If the results of these analyses suggest the presence of publication bias, we will further explore its potential impact using the trim and fill method.

Summary of evidence

The quality of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This will be independently completed by two researchers, and any disagreements will be resolved through discussion or by consulting a third researcher.

Ethics and dissemination

This study will not involve the collection or analysis of any individual patient data and therefore does not raise any ethical concerns related to the protection of personal privacy. As this study is based solely on the synthesis of published literature, no formal ethical review is required.

Patient and public involvement

This study will not involve the patients and/or the public in the design, conduct, reporting, or dissemination of the research.

Ethics statements

Patient consent for publication

Not applicable.

Author Contributions

Ying Yang and Yulan Luo designed this study. Menglin Tang serves as the supervisor of this study. The research strategy for each database will be designed by all review authors. Ying Yang and Ping Luo will independently carry out the search, selection, and identification of studies and the data extraction. Yulan Luo will perform the data synthesis and analysis. Jiarong Zeng will serve as the third author for the settlement of the disagreement. Xinmao Shi and Menglin Tang will be the advisers for methodology. All authors have approved the publication of this study protocol.

Competing interest

None declared.

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References

1 JT Giacino, CT Trott. Rehabilitative management of patients with disorders of consciousness: grand rounds. *J Head Trauma Rehabil* 2004;19(3):254-65.

2 VL Feigin, A Theadom, S Barker-Collo, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol* 2013;12(1):53-64.

3 MC Dewan, A Rattani, S Gupta, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018;130(4):1080-97.

4 Z Ye, Z Li, S Zhong, et al. The recent two decades of traumatic brain injury: a bibliometric analysis and systematic review. *Int J Surg* 2024;110(6):3745-59.

5 A Maas, DK Menon, PD Adelson, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017;16(12):987-1048.

6 N Stocchetti, M Carbonara, G Citerio, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017;16(6):452-64.

7 JT Giacino, JJ Fins, S Laureys, ND Schiff. Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol* 2014;10(2):99-114.

8 S Zarshenas, A Colantonio, SD Horn, S Jaglal, N Cullen. Cognitive and Motor Recovery and Predictors of Long-Term Outcome in Patients With Traumatic Brain Injury. *Arch Phys Med Rehabil* 2019;100(7):1274-82.

9 JH Adams, B Jennett, DR McLellan, LS Murray, DI Graham. The neuropathology of the vegetative state after head injury. *J Clin Pathol* 1999;52(11):804-06.

10 C Machado, M Estevez, R Redriguez, et al. Wakefulness and loss of awareness: brain and brainstem interaction in the vegetative state. *Neurology* 2010;75(8):751, 751-52.

11 TM Andriessen, J Horn, G Franschman, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma* 2011;28(10):2019-31.

12 Y Li, J Gu, J Zhou, et al. The epidemiology of traumatic brain injury in civilian inpatients of Chinese Military Hospitals, 2001-2007. *Brain Inj* 2015;29(7-8):981-88.

13 R Nakase-Richardson, J Tran, D Cifu, et al. Do rehospitalization rates differ among injury severity levels in the NIDRR Traumatic Brain Injury Model Systems program? *Arch Phys Med Rehabil* 2013;94(10):1884-90.

14 S Ganesh, A Guernon, L Chalcraft, et al. Medical comorbidities in disorders of consciousness patients and their association with functional outcomes. *Arch Phys Med Rehabil* 2013;94(10):1899-907.

15 J Whyte, R Nakase-Richardson. Disorders of consciousness: outcomes, comorbidities, and care needs. *Arch Phys Med Rehabil* 2013;94(10):1851-54.

16 J Whyte, AM Nordenbo, K Kalmar, et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. *Arch Phys Med Rehabil* 2013;94(10):1877-83.

17 JT Giacino, J Whyte, E Bagiella, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012;366(9):819-26.

18 C Chatelle, A Thibaut, O Gosseries, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. *Front Hum Neurosci* 2014;8:917.

19 M Corazzol, G Lio, A Lefevre, et al. Restoring consciousness with vagus nerve stimulation. *Curr Biol* 2017;27(18):R994-96.

20 ND Schiff, JT Giacino, K Kalmar, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 2007;448(7153):600-03.

21 JL Nickels, WN Schneider, ML Dombovy, TM Wong. Clinical use of amantadine in brain injury rehabilitation. *Brain Inj* 1994;8(8):709-18.

22 A Thibaut, N Schiff, J Giacino, S Laureys, O Gosseries. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol* 2019;18(6):600-14.

23 Y Zhou, H Yang, M You, Z Feng, X Dong. Cognition-Enhancement Effect of Median Nerve Electrical Stimulation in Patients with Cognitive Impairment: A Retrospective Cohort Study. *World Neurosurg* 2024;184:e537-45.

24 ST Tsai, WY Chuang, CC Kuo, et al. Dorsolateral subthalamic neuronal activity enhanced by median nerve stimulation characterizes Parkinson's disease during deep brain stimulation with general anesthesia. *J Neurosurg* 2015;123(6):1394-400.

25 X Wu, L Xie, J Lei, et al. Acute traumatic coma awakening by right median nerve electrical stimulation: a randomised controlled trial. *Intensive Care Med* 2023;49(6):633-44.

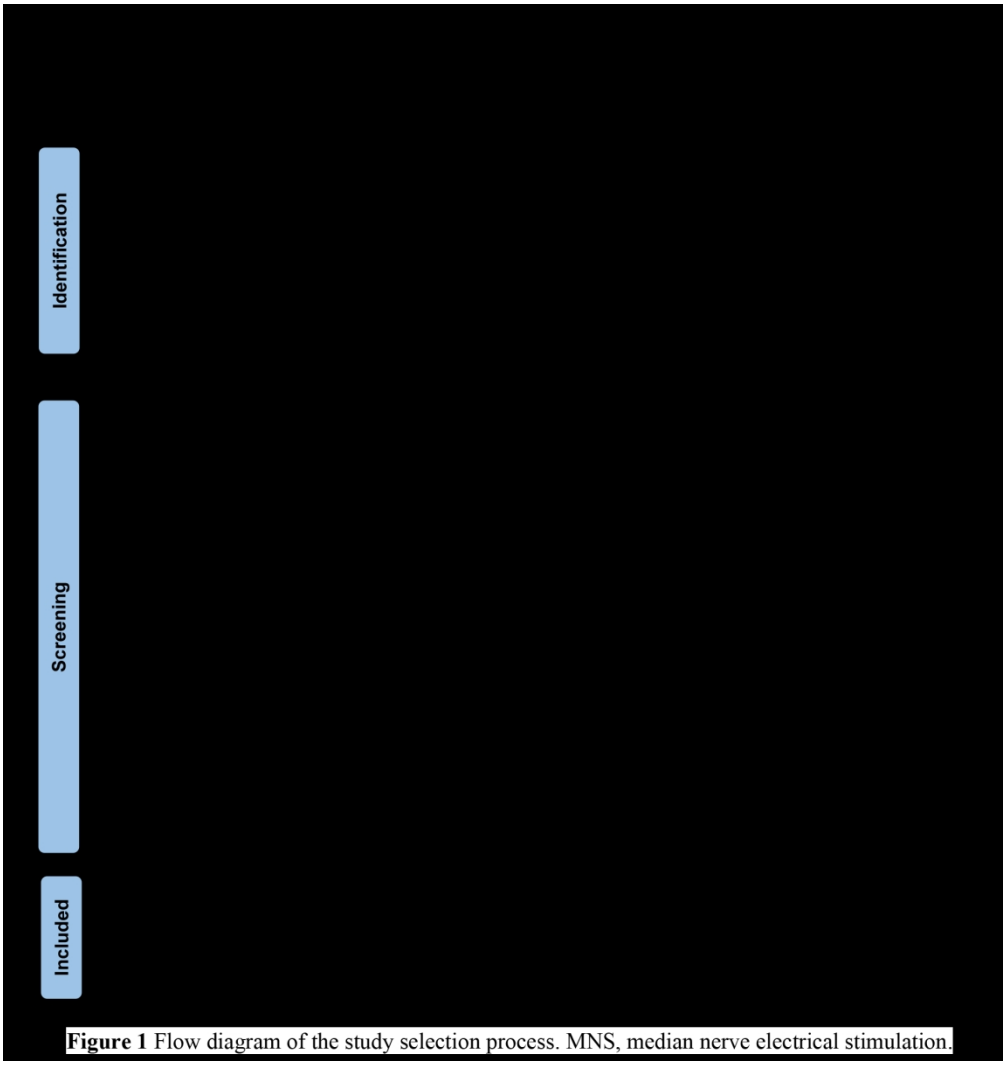
26 J Lei, L Wang, G Gao, E Cooper, J Jiang. Right Median Nerve Electrical Stimulation for Acute Traumatic Coma Patients. *J Neurotrauma* 2015;32(20):1584-89.

27 BL Edlow, L Sanz, L Polizzotto, et al. Therapies to Restore Consciousness in Patients with Severe Brain Injuries: A Gap Analysis and Future Directions. *Neurocrit Care* 2021;35(Suppl 1):68-85.

28 JT Liu, CH Wang, IC Chou, et al. Regaining consciousness for prolonged comatose patients with right median nerve stimulation. *Acta Neurochir Suppl* 2003;87:11-14.

29 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.

30 D Moher, L Shamseer, M Clarke, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.



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Complete List of Authors:	Yang, Ying; Sichuan University West China Hospital School of Nursing, Department of Critial Care Medicine Luo, Yulan; Sichuan University, Department of Critical Care Medicine Feng, Mei; Sichuan University, Department of Nursing Luo, Ping; Sichuan University, Department of Critical Care Medicine Zeng, Jiarong; Sichuan University, Department of Critical Care Medicine Shi, Xinmao; Sichuan University, Department of Critical Care Medicine Tang, Menglin; Sichuan University, Department of Cardiovascular Surgery
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Nursing, Complementary medicine, Evidence based practice
Keywords:	Brain Injuries, Electric Stimulation Therapy, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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Abstract

Strengths and limitations of this study

- This will be the first comprehensive systematic review and meta-analysis to evaluate the effects of MNES on the improvement of DOC following TBI.
- The independent dual-reviewer process for study selection and data extraction, with the involvement of a third reviewer to resolve any disagreements, serves to fortify the review's credibility and precision.

- The employment of Egger's and Begg's tests, coupled with the trim and fill method, will facilitate the assessment and mitigation of potential publication bias, thereby enhancing the robustness of the analysis.
- Given the potential disparities in methodological approaches, patient cohorts, and specifics of median nerve electrical stimulation protocols among the included studies, significant heterogeneity may arise, potentially impeding the aggregation and interpretation of results.

Introduction

Traumatic brain injury (TBI) is one of the prevalent critical illnesses encountered in clinical practice, often resulting in a spectrum of consciousness disorders among survivors. Prolonged states of impaired consciousness can significantly elevate the susceptibility to complications such as urinary tract infections and pulmonary issues, consequently leading to a compromised prognosis and substantially impacting the quality of life for affected individuals. Clinical studies have reported that median nerve electrical stimulation (MNES) may have a therapeutic effect in the treatment of disorders of consciousness (DOC). We plan to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of MNES in the management of DOC subsequent to TBI.

Methods and analysis

We will conduct a comprehensive literature search in the following electronic databases: Web of Science, Embase, PubMed, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), and Chinese Scientific Journal Database (VIP). The search will be performed from the inception of the databases until September 30, 2024. Furthermore, we will search for relevant ongoing trials in the

International Clinical Trial Registry Platform (ICTRP), ClinicalTrials.gov, and China Clinical Trial Registry (Chi-CRT). Grey literature will also be sourced from reputable sources like GreyNet International, Open Grey, and Google Scholar. We will include eligible randomized controlled trials (RCTs). The primary outcome of interest will be the assessment of consciousness disorder severity. To ensure rigor and consistency, two independent reviewers will screen the studies for inclusion, extract relevant data, and assess the risk of bias. Any discrepancies will be resolved through discussion or consultation with a third reviewer. The quality of evidence will be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Data synthesis and meta-analysis will be conducted using STATA 15.1 software.

Ethics and dissemination

This systematic review and meta-analysis does not involve the collection or use of any individual patient data, thereby obviating the necessity for ethical review. The research findings will be disseminated through publication in peer-reviewed scientific journals.

PROSPERO registration number

CRD42024533359.

Keywords:

Median nerve electrical stimulation, Traumatic brain injury, Disorders of consciousness, Systematic review and meta-analysis.

Introduction

Traumatic brain injury (TBI) arises from external mechanical forces affecting the brain, potentially resulting in enduring or transitory cognitive, physical, and psychological function impairments. Importantly, TBI frequently coincides with changes in consciousness and stands as a substantial contributor to mortality and disability.[1-2]. Every year, 69 million people worldwide suffer from TBI[3], with a mortality rate of 20% -30%[4]. Furthermore, it is projected to remain the leading cause of neurological disability by 2031[5], posing a significant public health burden globally. In recent years, progressions in emergency medicine and intensive care technologies have bolstered the survival rates of individuals afflicted by TBI[6]. Nevertheless, many individuals enduring severe TBI may encounter disorders of consciousness (DOC), including coma, vegetative state (VS)/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS)[7]. Prolonged consciousness disorders not only result in substantial economic burdens but also impart significant mental and emotional strain on the patients' families and society as a whole[8].

DOC following TBI is associated with widespread functional changes caused by focal brain injury or more comprehensive neural damage[79]. This encompasses damage to the brainstem reticular ascending activation system (ARAS), disturbances in neurotransmitters crucial for sustaining the sleep-wake cycle, and widespread lesions in the cerebral cortex. Following ARAS injury, pivotal for governing the human sleep-wake cycle, individuals may endure prolonged periods of unconsciousness.[10]

Research has shown that up to 14% of TBI patients experience long-term coma or persistent VS, and the longer the coma duration, the higher the mortality rate[11-12].The incidence of medical complications in patients with prolonged DOC is high[13], including muscle tone

hyperactivity, sleep disorders, urinary tract infections, hydrocephalus, and pneumonia. Such complications can detrimentally influence the rehabilitation trajectory, quality of life, and mortality rate[14-15]. Reducing the duration of DOC could potentially enhance outcomes and increase patient participation in rehabilitation therapy[16]. Therefore, identifying methods to expedite the awakening process and reduce the risk of long-term disability in TBI patients with DOC has become a crucial issue in the field of neurological rehabilitation research.

Present treatment strategies aimed at fostering the recuperation of DOC subsequent to TBI include pharmacological interventions, such as amantadine and zolpidem[17-18], as well as invasive brain stimulation therapies, including vagus nerve stimulation and deep brain stimulation[19-20]. However, current evidence inadequately substantiates the enduring or prolonged efficacy of these therapeutic approaches. Additionally, the potential adverse reactions associated with medications and invasive procedures, such as heightened susceptibility to infections and disease exacerbation[21-22], curtail their widespread clinical utility, confining them primarily to supplementary roles. In recent years, the exploration of non-invasive stimulation technologies to expedite awakening has garnered attention as a focal point in this domain. As a non-invasive physical therapy method, MNES has been widely utilized for various nerve-related conditions due to its demonstrated therapeutic benefits[23-24]. Some clinical trials have also reported that MNES may be a potential intervention to accelerate the recovery from DOC following TBI[25-26]. MNES involves the placement of electrodes on the median nerve for electrical stimulation, eliciting central excitatory effects. This process reactivates suppressed neurons and the Ascending Reticular Activating System (ARAS), enhances blood perfusion, and elevates brain-derived neurotrophic factor levels, thereby fostering the awakening process.[27-28].

However, a systematic evaluation of the clinical evidence concerning the effectiveness and safety of MNES in the management of DOC subsequent to TBI is currently absent. This systematic review and meta-analysis aims to provide a comprehensive, evidence-based assessment of the potential benefits and risks of MNES as an intervention for awakening in TBI patients.

Methods

This study will be conducted in strict accordance with the *Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines*[29-30]. The study is scheduled to begin on September 30, 2024, and is expected to be completed by June 30, 2025.

Inclusion criteria

Types of studies

This study will only include randomized controlled trials (RCTs), without any language or regional restrictions. Non-clinical research types, such as cohort studies, purely theoretical studies, case reports, editorials, commentaries, or expert opinions, will be excluded from the analysis.

Types of participants

The population of interest for this systematic review will be adult patients (aged 18 years and above, with no gender restrictions) diagnosed with DOC subsequent to closed TBI.

Patients will be excluded if they exhibit any of the following conditions: unstable vital signs, history of epilepsy, pregnancy, severe arrhythmias, or the presence of a pacemaker.

Types of interventions and comparisons

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.

Types of outcomes

Primary outcomes

The proportion of patients who regained consciousness after 6 months.

Secondary outcomes

1. Clinical Behavior Checklist for Evaluating Consciousness Disorders

Glasgow Coma Scale (GCS), Coma Recovery Scale-Revised (CRS-R), Wessex Head Injury Matrix (WHIM), and Full Outline of UnResponsiveness (FOUR).

2. Disability Rating Scale (DRS)

3. Incidence of complications

4. Electrophysiological and neuroimaging evaluation.

5. Incidence of adverse events (AEs).

Information sources

Electronic databases

We will conduct a comprehensive literature search in the following electronic databases: Web of Science, Embase, PubMed, Cochrane Library, China Biology Medicine (CBM), China

National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), and Chinese Scientific Journal Database (VIP). The search will encompass the databases from their inception to September 30, 2024. Furthermore, we will manually scrutinize the reference lists of the retrieved articles to identify any potentially eligible studies. No constraints will be imposed on language or publication status.

Other resources

In addition to the electronic database searches, we will comprehensively explore clinical trial registration platforms to pinpoint any ongoing or unpublished trials relevant to our review. These platforms will include the World Health Organization's International Clinical Trial Registration Platform, ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and the Cochrane Central Register of Controlled Trials. Furthermore, we will search for valuable grey literature through specialized websites, such as GreyNet International, OpenGrey, and Google Scholar. This methodology aims to uncover additional relevant studies that may not have been published in the peer-reviewed literature, thereby reducing the risk of publication bias and enhancing the completeness of our systematic review.

Search strategy

To ensure the rigor and accuracy of the literature search, we will construct a comprehensive search strategy based on the PICOS framework. This strategy will incorporate subject-specific keywords and free-text terms to encompass all relevant studies. As an example, the detailed search strategy for the PubMed database is presented in **Table 1**.

Table 1 Search strategy for PubMed

Sequence	Items
#1	Brain Injuries, Traumatic (MeSH)

#2	Traumatic Brain Injuries
#3	Trauma, Brain
#4	Brain Trauma
#5	Brain Traumas
#6	Traumas, Brain
#7	Traumatic Brain Injury
#8	Encephalopathy, Traumatic
#9	Encephalopathies, Traumatic
#10	Traumatic Encephalopathies
#11	Injury, Brain, Traumatic
#12	Traumatic Encephalopathy
#13	TBI
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	Coma (MeSH)
#16	Comas
#17	Comatose
#18	Consciousness Disorders (MeSH)
#19	Consciousness Disorder
#20	Disorder of Consciousness
#21	Disorders of Consciousness
#22	Consciousness, Level Depressed
#23	Depressed Level of Consciousness
#24	Consciousness, Level Altered
#25	Altered Level of Consciousness
#26	Semiconsciousness
#27	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	Electric Stimulation Therapy (MeSH)
#29	Therapy, Electric Stimulation
#30	Stimulation Therapy, Electric
#31	Electrotherapy
#32	Therapeutic Electric Stimulation
#33	Electric Stimulation, Therapeutic
#34	Stimulation, Therapeutic Electric
#35	Electrical Stimulation Therapy
#36	Stimulation Therapy, Electrical
#37	Therapy, Electrical Stimulation
#38	Therapeutic Electrical Stimulation
#39	Electrical Stimulation, Therapeutic
#40	Stimulation, Therapeutic Electrical
#41	Interferential Current Electrotherapy
#42	Electrotherapy, Interferential Current

#43	Transcutaneous Electric Nerve Stimulation
#44	Electroacupuncture
#45	Median nerve electrical stimulation
#46	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47	Clinical trials (MeSH)
#48	Randomized Clinical trials
#49	Randomized
#50	Random
#51	Placebo
#52	Trial
#53	Groups
#54	#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#55	#14 AND #27 AND #46 AND #54

Selection of studies

Two independent researchers will initially screen the titles and abstracts of the retrieved literature to exclude irrelevant studies. Subsequently, They will then thoroughly review the full-text articles to determine eligibility based on the predefined inclusion and exclusion criteria. Any disagreements will be discussed and resolved with the third researcher. The selection process is shown in Figure 1.

Data extraction

Two independent research teams will extract data from the included studies using a pre-designed data extraction table. The information to be collected will include the first author, publication year, nationality, sample size of experimental and control groups, participant characteristics (age, gender, comorbidities, etc.), details of the intervention (stimulation parameters, treatment duration, and course), outcome measures (consciousness assessment scales, disability rating scales, reported adverse events, etc.). The data extraction process will be independently carried out by the two research teams. Any discrepancies or disagreements t

arising during this phase will be resolved through discussion and consultation with a third researcher if necessary.

Risk of bias assessment

The risk of bias assessment for the included studies will be conducted based on the Cochrane Systematic Review Manual (version 5.1.0). The following key domains will be evaluated: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, completeness of outcome data, selective reporting, and other potential sources of bias. Each domain will be judged as having a low risk of bias, an unclear risk of bias, or a high risk of bias, according to the predefined criteria outlined in the Cochrane Handbook. Any disagreements will be discussed and resolved with the third researcher.

Data synthesis

The data analysis will be conducted using Stata version 15.0. For continuous data, we will use the standardized mean difference (SMD) and 95% confidence intervals (95%CI) to quantify the effect sizes. For dichotomous data, we will calculate the odds ratio (OR) and 95% CI to estimate the treatment effects. Statistical significance will be determined based on whether the 95% CI of the SMD does not include 0 or the 95% CI of the OR does not include 1. If the 95% CI does not encompass these values, the difference will be considered statistically significant.

Assessment of heterogeneity

The assessment of heterogeneity will be conducted using the I^2 statistic. If the $I^2 < 50\%$ with the $P > 0.1$, the heterogeneity across the included studies will be considered low. In such cases, a fixed-effects model will be used to perform the meta-analysis calculations. However, if the $I^2 > 50\%$ or $P \leq 0.1$, significant heterogeneity will be present. In this scenario, sensitivity analyses and subgroup analyses will be performed to explore the potential sources of

heterogeneity. If the subgroup analyses are unable to adequately address the observed heterogeneity, a random-effects model will be used for the meta-analysis calculations.

Sensitivity analysis

To assess the robustness of the meta-analysis results, we will conduct a sensitivity analysis by sequentially removing each study from the analysis and re-estimating the overall effect size.

Subgroup analysis

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.

Assessment of publication bias

To assess the potential presence of publication bias, we will conduct Egger's linear regression test and Begg's rank correlation test. If the results of these analyses suggest the presence of publication bias, we will further explore its potential impact using the trim and fill method.

Summary of evidence

The quality of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This will be independently completed by two researchers, and any disagreements will be resolved through discussion or by consulting a third researcher.

Ethics and dissemination

This study will not involve the collection or analysis of any individual patient data and therefore does not raise any ethical concerns related to the protection of personal privacy. As this study is based solely on the synthesis of published literature, no formal ethical review is required. The results of the study will be published in peer-reviewed journals.

Patient and public involvement

This study will not involve the patients and/or the public in the design, conduct, reporting, or dissemination of the research.

Ethics statements

Patient consent for publication

Not applicable.

Author Contributions

Ying Yang and Yulan Luo designed this study. Menglin Tang serves as the supervisor of this study. The research strategy for each database will be designed by all review authors. Ying Yang and Ping Luo will independently carry out the search, selection, and identification of studies and the data extraction. Yulan Luo and Mei Feng will perform the data synthesis and analysis. Jiarong Zeng will serve as the third author for the settlement of the disagreement. Xinmao Shi and Menglin Tang will be the advisers for methodology. All authors have approved the publication of this study protocol. Ying Yang is the guarantor.

Competing interest

None declared.

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Figure legends

Figure 1. Flow diagram of the study selection process. MNS, median nerve electrical stimulation.

References

1 JT Giacino, CT Trott. Rehabilitative management of patients with disorders of consciousness: grand rounds. *J Head Trauma Rehabil* 2004;19(3):254-65.

2 VL Feigin, A Theadom, S Barker-Collo, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol* 2013;12(1):53-64.

3 MC Dewan, A Rattani, S Gupta, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018;130(4):1080-97.

4 Z Ye, Z Li, S Zhong, et al. The recent two decades of traumatic brain injury: a bibliometric analysis and systematic review. *Int J Surg* 2024;110(6):3745-59.

5 A Maas, DK Menon, PD Adelson, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017;16(12):987-1048.

6 N Stocchetti, M Carbonara, G Citerio, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017;16(6):452-64.

7 JT Giacino, JJ Fins, S Laureys, ND Schiff. Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol* 2014;10(2):99-114.

8 S Zarshenas, A Colantonio, SD Horn, S Jaglal, N Cullen. Cognitive and Motor Recovery and Predictors of Long-Term Outcome in Patients With Traumatic Brain Injury. *Arch Phys Med Rehabil* 2019;100(7):1274-82.

9 JH Adams, B Jennett, DR McLellan, LS Murray, DI Graham. The neuropathology of the vegetative state after head injury. *J Clin Pathol* 1999;52(11):804-06.

10 C Machado, M Estevez, R Redriguez, et al. Wakefulness and loss of awareness: brain and brainstem interaction in the vegetative state. *Neurology* 2010;75(8):751, 751-52.

11 TM Andriessen, J Horn, G Franschman, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma* 2011;28(10):2019-31.

12 Y Li, J Gu, J Zhou, et al. The epidemiology of traumatic brain injury in civilian inpatients of Chinese Military Hospitals, 2001-2007. *Brain Inj* 2015;29(7-8):981-88.

13 R Nakase-Richardson, J Tran, D Cifu, et al. Do rehospitalization rates differ among injury severity levels in the NIDRR Traumatic Brain Injury Model Systems program? *Arch Phys Med Rehabil* 2013;94(10):1884-90.

14 S Ganesh, A Guernon, L Chalcraft, et al. Medical comorbidities in disorders of consciousness patients and their association with functional outcomes. *Arch Phys Med Rehabil* 2013;94(10):1899-907.

15 J Whyte, R Nakase-Richardson. Disorders of consciousness: outcomes, comorbidities, and care needs. *Arch Phys Med Rehabil* 2013;94(10):1851-54.

16 J Whyte, AM Nordenbo, K Kalmar, et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. *Arch Phys Med Rehabil* 2013;94(10):1877-83.

17 JT Giacino, J Whyte, E Bagiella, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012;366(9):819-26.

18 C Chatelle, A Thibaut, O Gosseries, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. *Front Hum Neurosci* 2014;8:917.

19 M Corazzol, G Lio, A Lefevre, et al. Restoring consciousness with vagus nerve stimulation. *Curr Biol* 2017;27(18):R994-96.

20 ND Schiff, JT Giacino, K Kalmar, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 2007;448(7153):600-03.

21 JL Nickels, WN Schneider, ML Dombovy, TM Wong. Clinical use of amantadine in brain injury rehabilitation. *Brain Inj* 1994;8(8):709-18.

22 A Thibaut, N Schiff, J Giacino, S Laureys, O Gosseries. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol* 2019;18(6):600-14.

23 Y Zhou, H Yang, M You, Z Feng, X Dong. Cognition-Enhancement Effect of Median Nerve Electrical Stimulation in Patients

with Cognitive Impairment: A Retrospective Cohort Study. *World Neurosurg* 2024;184:e537-45.

24 ST Tsai, WY Chuang, CC Kuo, et al. Dorsolateral subthalamic neuronal activity enhanced by median nerve stimulation characterizes Parkinson's disease during deep brain stimulation with general anesthesia. *J Neurosurg* 2015;123(6):1394-400.

25 X Wu, L Xie, J Lei, et al. Acute traumatic coma awakening by right median nerve electrical stimulation: a randomised controlled trial. *Intensive Care Med* 2023;49(6):633-44.

26 J Lei, L Wang, G Gao, E Cooper, J Jiang. Right Median Nerve Electrical Stimulation for Acute Traumatic Coma Patients. *J Neurotrauma* 2015;32(20):1584-89.

27 BL Edlow, L Sanz, L Polizzotto, et al. Therapies to Restore Consciousness in Patients with Severe Brain Injuries: A Gap Analysis and Future Directions. *Neurocrit Care* 2021;35(Suppl 1):68-85.

28 JT Liu, CH Wang, IC Chou, et al. Regaining consciousness for prolonged comatose patients with right median nerve stimulation. *Acta Neurochir Suppl* 2003;87:11-14.

29 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.

30 D Moher, L Shamseer, M Clarke, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

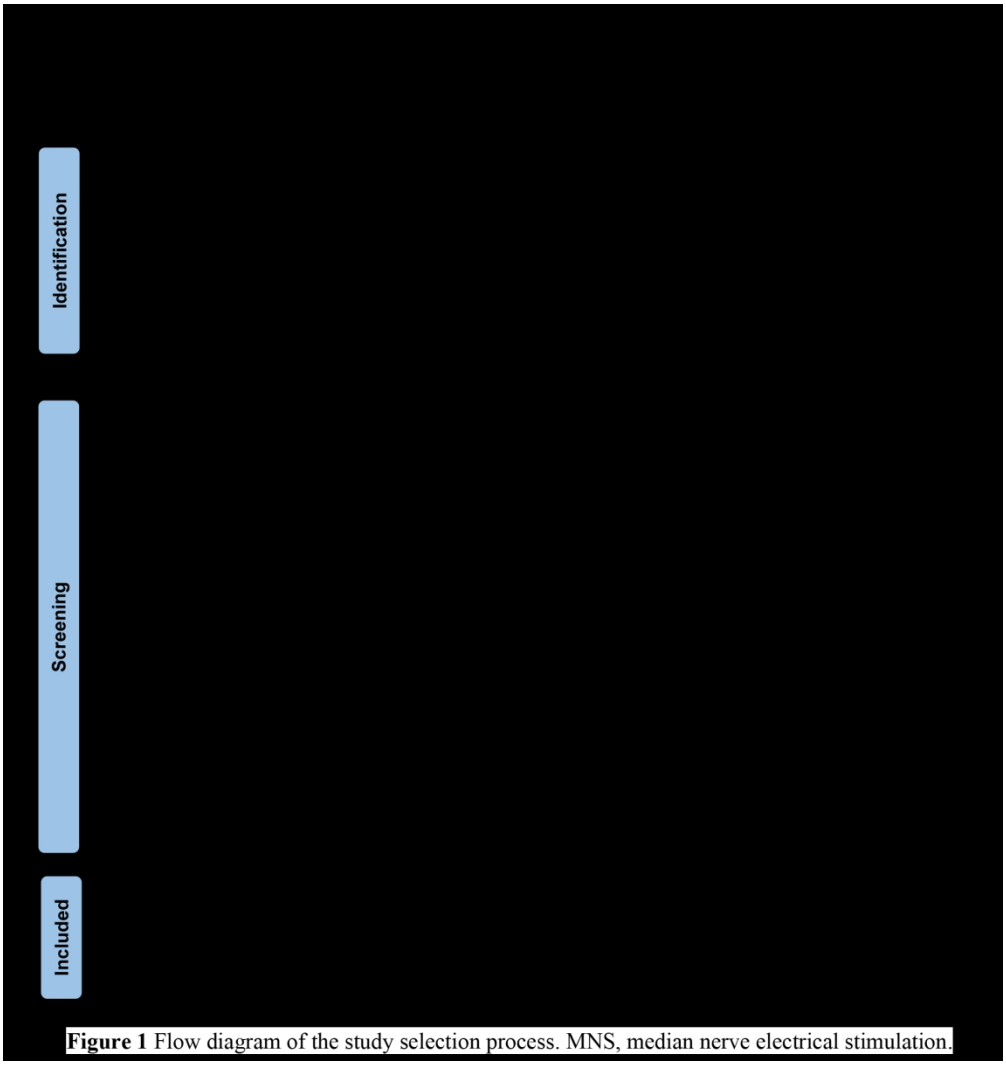

Figure 1 Flow diagram of the study selection process. MNS, median nerve electrical stimulation.

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