INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Neuroprotection by Transcranial Direct Current Stimulation in Rodent Models of Focal Ischemic Stroke: A Meta-analysis

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Review question / Objective: **Does transcranial direct current stimulation have a neuroprotection effect in rodent models of focal ischemic stroke?**
Condition being studied: **Focal ischemic stroke.**
Information sources: We have searched the following electronic bibliographic databases: MEDLINE (via PubMed), EMBASE, Web of Science, and Scopus. No publication date restrictions. In cases when data was not explicitly reported, we will extract data from figures using Engauge Digitizer. In cases of ambiguity, authors were contacted to provide additional information. Missing data items will not be requested from authors as the data has not been peer-reviewed.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 May 2021 and was last updated on 20 May 2021 (registration number INPLASY202150080).

INTRODUCTION

Review question / Objective: **Does transcranial direct current stimulation have a neuroprotection effect in rodent models of focal ischemic stroke?**

Rationale: **Stroke, a leading cause of mortality, leads to over 2 million new cases annually and is associated with the highest disability-adjusted life-years lost of any disease in China. Approximately 80% of all strokes result from ischemic stroke. Due to the narrow treatment time window, current**

therapeutic options remain limited, including intravenous administration of recombinant tissue plasminogen activator and endovascular intervention. Several advances have been made in declining stroke mortality, but it remains a leading cause of disability in up to 50% of sufferers. Infarct size has been linked with stroke severity in clinical investigations. Therefore, reducing infarct size has become an important target and research hotspot in the treatment of ischemic stroke. Transcranial direct current stimulation is a non-invasive, easy to administer, safe, and well-tolerated technique that has received growing interest owing to its potential efficacy in modulating plasticity in healthy persons and patients. In order to comprehensively and systematically understand the effect of transcranial direct current stimulation in reducing infarct size and improving neurological deficit in ischemic stroke, a meta-analysis was conducted. Once the benefits are proven, it will provide a useful reference for clinical use in the future.

Condition being studied: Focal ischemic stroke.

METHODS

Search strategy: We have searched the following electronic bibliographic databases: MEDLINE (via PubMed), EMBASE, Web of Science, and Scopus. No publication date restrictions. The language was limited to English. The search string was built as follows: individually or combined included stroke, transcranial direct current stimulation, and a string of words that were determined after multiple pre-searches.

Participant or population: Focal ischemic stroke rodent models.

Intervention: transcranial direct current stimulation only, with unlimited polarity, density of current, duration, and timing of application.

Comparator: Sham transcranial direct current stimulation or blank treatment.

Study designs to be included: Controlled studies with a separate control group

Eligibility criteria: (1) Focal ischemic stroke rodent models, regardless of the modeling method; (2) The intervention group was treated with transcranial direct current stimulation, which had definite anodal and cathodal electrodes and was not delivered in conjunction with another therapy, with unlimited polarity, density of current, duration, and timing of application. Interventions for control group were sham transcranial direct current stimulation or blank treatment; (3) The primary outcome was infarct size, regardless of the method of evaluation, which can be magnetic resonance imaging (MRI), tetrazolium chloride (TTC), cresyl violet, etc. Infarct size can be recorded as a percentage of the hemisphere, percentage of the whole brain, in cm^2, or in mm^3. The secondary outcomes included neurobehavioural outcomes as assessed by a modified neurological severity score, mortality, and adverse events; (4) Literature is publised in English; (5) Original full research paper, not review, editorial, and conference abstract.

Information sources: We have searched the following electronic bibliographic databases: MEDLINE (via PubMed), EMBASE, Web of Science, and Scopus. No publication date restrictions. In cases when data was not explicitly reported, we will extract data from figures using Engauge Digitizer. In cases of ambiguity, authors were contacted to provide additional information. Missing data items will not be requested from authors as the data has not been peer-reviewed.

Main outcome(s): The primary outcome was infarct size, regardless of the method of evaluation, which can be magnetic resonance imaging (MRI), tetrazolium chloride (TTC), cresyl violet, etc. Infarct size can be recorded as a percentage of the hemisphere, percentage of the whole brain, in cm^2, or in mm^3.

Additional outcome(s): The secondary outcomes included neurobehavioural outcomes as assessed by a modified

neurological severity score, mortality, and adverse events.

Quality assessment / Risk of bias analysis: The SYRCLE animal experiment bias risk assessment tool will be applied to evaluate the risk of bias in individual included studies. Two investigators will independently read the included literature and assessed the risk of bias. Discrepancies will be resolved through discussion, or by consulting a third investigator. Studies will be divided into low-bias risk, high-bias risk and unclear-bias risk.

Strategy of data synthesis: Meta-analysis will be performed using Review Manager (RevMan) software (The Cochrane Collaboration, version 5.3). For continuous variables, a standardized mean difference (SMD) will be calculated using random-effects inverse variance meta-analyses and presented with 95% confidence intervals if measurement methods were different among the included studies; otherwise, a mean difference (MD) will be calculated. Anodal and cathodal trials will be analyzed separately. The results of the meta-analysis will be presented using forest plots. The I^2 will be used for evaluating heterogeneity. If meta-analysis is not possible, data will be reported through a descriptive summary.

Subgroup analysis: If the necessary data are available, subgroup analyses will be done to determine whether the effect of transcranial direct current stimulation varied by the duration of ischemia and anesthesia used for the intervention procedure.

Sensitivity analysis: Leave-one-out sensitivity analyses excluding data from individual studies were conducted to assess the robustness of findings.

Language: English.

Country(ies) involved: China.

Keywords: Transcranial Direct Current Stimulation; Ischemic stroke; Rodent model; Cerebral infarction; Meta-analysis.

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