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Comparison of neuroprotective adjuvant treatments in patients with acute ischemic stroke after reperfusion therapy: A systematic review and network meta-analysis

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Corresponding author:
Yi-Hsiang Chen

ck951250@gmail.com

Author Affiliation:
Keelung Chang Gung Memorial Hospital.

Chen, YH; Huang, WY; Wei, YC; Lee, M.

ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 October 2024 and was last updated on 28 October 2024.

INTRODUCTION

Review question / Objective Participants (P): Adults with acute ischemic stroke receiving reperfusion therapy. Interventions (I): Various neuroprotective treatments used in conjunction with reperfusion therapy. Comparisons (C): Comparison of neuroprotective interventions against each other and standard care. Outcomes (O): Primary: Functional recovery(90days mRS), Secondary: mortality rates, and incidence of symptomatic intracerebral hemorrhage (sICH). Study Design (S): Randomized controlled trials (RCTs) evaluating neuroprotective interventions in AIS patients.

Rationale Acute ischemic stroke (AIS) is a leading cause of mortality and long-term disability globally. Despite the effectiveness of reperfusion therapies in restoring blood flow, many patients experience suboptimal recovery due to secondary injury caused by complex biochemical and cellular cascades following ischemia. Neuroprotective treatments, such as pharmacological agents and hypothermia, aim to reduce this secondary injury and improve outcomes but have shown inconsistent results in trials. A comprehensive network meta-analysis is needed to evaluate and rank the efficacy of these neuroprotective adjuvants in AIS, providing guidance for optimal treatment strategies alongside reperfusion therapy.

Condition being studied Acute ischemic stroke (AIS) is a medical condition resulting from a sudden blockage in the blood vessels supplying the brain, leading to reduced blood flow and oxygen deprivation in brain tissue. AIS is one of the leading causes of death and long-term disability worldwide, often resulting in severe neurological impairments and a diminished quality of life for survivors. Treatment primarily focuses on reperfusion therapies, such as intravenous thrombolysis and mechanical thrombectomy, to restore blood flow. However, many AIS patients continue to experience poor functional recovery due to secondary injury, highlighting the need for additional neuroprotective strategies to improve outcomes.

METHODS

Search strategy A comprehensive search was conducted across PubMed, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov databases using the following keywords: "acute ischemic stroke," "neuroprotective adjuvant treatments," "thrombolysis or thrombectomy," and "randomized." This strategy is designed to support a systematic review and network meta-analysis, capturing studies on neuroprotective adjuvants used alongside reperfusion therapies for acute ischemic stroke.

Participant or population This review will focus on patients diagnosed with acute ischemic stroke (AIS) who have received reperfusion therapy, specifically intravenous thrombolysis, mechanical thrombectomy, or a combination of both. The population includes adult patients across all age groups and diverse demographic backgrounds, without restrictions on stroke severity at presentation. Studies that investigate the use of neuroprotective adjuvant treatments alongside reperfusion therapy to improve functional outcomes, reduce mortality, or minimize complications will be included.

Intervention The neuroprotective adjuvant treatments evaluated in this review are divided into two main categories:
Pharmacological Interventions – These include neuroprotective drugs such as cerebrolysin, butylphthalide (NBP), 3K3A-activated protein C (APC), otaplimastat, nerinetide (NA-1), uric acid (UA), ApTOLL, and nelonemdaz (Neu200). These pharmacological agents aim to reduce ischemic damage, protect neuronal function, and enhance recovery outcomes when used alongside reperfusion therapy.
Non-Pharmacological Interventions – These include treatments such as regional hypothermia, normobaric oxygen therapy (NBO), and remote ischemic conditioning (RIC). These approaches leverage hypothermia, oxygenation, or conditioning techniques to protect brain tissue and mitigate secondary injury post-stroke.

Comparator The comparator in this review will be standard reperfusion therapy alone, which includes intravenous thrombolysis and/or mechanical thrombectomy without any neuroprotective adjuvant treatments. Studies that compare each neuroprotective intervention against this standard treatment, or against other neuroprotective interventions, will be included to assess the additional efficacy and safety of neuroprotective adjuvants in improving functional outcomes and reducing complications in acute ischemic stroke patients.

Study designs to be included This review will include randomized controlled trials (RCTs) as the primary study design to assess the efficacy and safety of neuroprotective adjuvant treatments in acute ischemic stroke patients undergoing reperfusion therapy. Only studies with a parallel-group design that compare neuroprotective interventions (pharmacological or non-pharmacological) to standard reperfusion therapy, or to other neuroprotective interventions, will be eligible. Other study designs, such as observational studies or case reports, will be excluded to ensure high-quality evidence for the network meta-analysis.

Eligibility criteria Inclusion criteria for the review consisted of: (1) randomized controlled trials (RCTs) that enrolled patients who received reperfusion treatments after acute ischemic stroke, including intravenous (IV) thrombolysis and/or intra-arterial (IA) thrombectomy; (2) RCTs that quantitatively assessed outcomes of neuroprotective adjuvant therapies, specifically neurological function (measured by the mRS), mortality, and incidence of symptomatic intracerebral hemorrhage (ICH); (3) a control group that received no neuroprotective adjuvant intervention or standard care; and (4) trials with available data on neurological function post-intervention at 90 days.
The choice of a 90-day evaluation period was informed by an initial literature review, identifying this timeframe as the most used follow-up across included studies. A standardized 90-day period was deemed essential to establish a benchmark for comparing the effectiveness of various neuroprotective adjuvant therapies. This led to a focus on this specific duration and exclusion of less consistently represented timeframes in the literature.
Exclusion criteria included: (1) non-randomized controlled trials; (2) studies in which participants did not receive reperfusion therapy; (3) studies lacking quantitative assessments of neurological function, mortality, or incidence of symptomatic intracranial hemorrhage (sICH); (4) studies with incomplete or unavailable data; and (5) studies with participant overlap from previously included trials.

Information sources The following information sources will be utilized for this review:
Electronic Databases: Comprehensive searches will be conducted in key electronic databases, including:

PubMed: For biomedical literature, including clinical studies and reviews.
EMBASE: For its extensive coverage of pharmacological and medical literature.
Cochrane CENTRAL: To access systematic reviews and trials relevant to neuroprotective treatments in acute ischemic stroke.
ClinicalTrials.gov: To identify ongoing and completed clinical trials focusing on neuroprotective adjuvant therapies.
Trial Registers: Additional searches will be performed in international clinical trial registers to locate unpublished or ongoing studies that may not yet be available in the electronic databases.
Contact with Authors: Authors of relevant studies may be contacted for additional data or clarification on study findings if needed.
Grey Literature: Searches will include grey literature, such as conference proceedings, theses, and reports, to capture studies that may not be published in traditional academic journals.
Reference Lists: The reference lists of included studies and relevant systematic reviews will be examined to identify any additional studies that meet the inclusion criteria.

Main outcome(s) The primary outcomes of this review will focus on the efficacy and safety of neuroprotective adjuvant treatments in acute ischemic stroke patients receiving reperfusion therapy. The outcomes to be assessed include:
Neurological Function:
Measured using the modified Rankin Scale (mRS) at 90 days post-intervention, which ranges from 0 (no symptoms) to 6 (death). Improvement in mRS scores will indicate better functional outcomes.
Mortality:
The overall mortality rate will be evaluated at 90 days post-intervention, comparing the number of deaths in the neuroprotective treatment group versus the control group.
Incidence of Symptomatic Intracerebral Hemorrhage (sICH):
The occurrence of symptomatic ICH will be assessed within 90 days of the intervention. This outcome will measure the safety profile of the neuroprotective treatments.
Effect Measures:
For neurological function, the mean difference in mRS scores between groups will be calculated, with lower scores indicating better outcomes.
Mortality will be expressed as a risk ratio (RR) to compare the proportion of deaths in both groups.
The incidence of sICH will also be reported as a risk ratio (RR) to determine the relative risk associated with neuroprotective adjuvants compared to standard care.

Additional outcome(s) In addition to the primary outcomes, the review will assess several secondary outcomes to provide a more comprehensive evaluation of neuroprotective adjuvant treatments in acute ischemic stroke patients:
Quality of Life:
Assessed using validated scales such as the EuroQol-5D (EQ-5D) or the Short Form Health Survey (SF-36) at 90 days post-intervention. Improvement in quality of life scores will indicate better overall well-being and functional status.
Length of Hospital Stay:
The total duration of hospitalization will be compared between the neuroprotective treatment group and the control group. A shorter length of stay may suggest better recovery and reduced healthcare resource utilization.
Functional Independence:
The proportion of patients achieving functional independence (mRS scores of 0–2) at 90 days post-intervention will be recorded. This will help evaluate the effectiveness of neuroprotective adjuvants in promoting independence in daily activities.
Recurrence of Stroke:
The incidence of recurrent stroke events within 90 days post-intervention will be analyzed to assess the long-term safety of neuroprotective treatments.
Adverse Events:
The overall incidence of adverse events associated with neuroprotective adjuvants, including but not limited to systemic side effects or other complications, will be documented to evaluate safety profiles.

Data management To manage records and data for this review, a systematic approach will be employed using Excel, EndNote, and MetaInsight for data analysis.
Record Management:
All identified studies from electronic databases, trial registers, and grey literature will be imported into EndNote for reference management. This will facilitate organization, deduplication, and tracking of records.
The references will then be exported from EndNote in CSV format to Excel for further data extraction and management.
Screening and Selection:
Duplicate records will be identified and removed in EndNote before exporting to Excel. The remaining records will be screened for eligibility based on the predefined inclusion and exclusion criteria. This screening process will be documented in Excel, ensuring transparency and reproducibility.
Data Extraction:

A structured Excel template will be used to extract relevant data from each included study. This template will contain specific columns for study characteristics, intervention details, outcomes assessed, sample sizes, and results. Using Excel will ensure consistency and organization in the data.
Data Analysis:
The extracted data in CSV format will then be imported into MetaInsight, an online platform designed for network meta-analysis. MetaInsight will be utilized to conduct statistical analyses, including calculating effect sizes and assessing heterogeneity across studies.
Results will be visually represented through network diagrams, forest plots, and other relevant graphics, facilitating clear interpretation and presentation of findings.
Quality Control:
To ensure accuracy and completeness, a second reviewer will independently check the data extraction process. Any discrepancies will be resolved through discussion, maintaining the integrity of the data.
Data Storage:
All records, data files, and analysis outputs will be securely stored in a password-protected folder, with regular backups to prevent data loss. This will ensure confidentiality and integrity throughout the review process.

Quality assessment / Risk of bias analysis The quality assessment of primary studies in this review will adhere to established guidelines to ensure robust findings.
Assessment of Publication Bias:
Publication bias will be evaluated using Egger's regression test, which quantifies asymmetry in the study distribution, following the Cochrane Handbook for Systematic Reviews of Interventions. A funnel plot will be generated using R (version 4.4.1) to visually assess potential bias by plotting the standard error against the risk difference.
Methodological Quality Assessment:
The Cochrane Risk of Bias Tool for Randomized Trials (version 2, RoB 2) will be used to assess the methodological quality of included studies. This tool evaluates six key components:
Randomization Process
Adherence to the Intervention
Handling of Missing Outcome Data
Outcome Measurement
Selective Reporting
Overall Risk of Bias
Visual Representation:
Risk-of-bias assessments will be visually represented using robvis (https://mcguinlu.shinyapps.io/robvis/), including a traffic-light plot and a summary plot to illustrate the findings clearly.

Strategy of data synthesis The data synthesis for this review will follow a systematic approach to analyze and integrate findings from the included studies. The strategy encompasses several key steps:
Data Preparation:
Extracted data from each study will be organized into an Excel spreadsheet. This spreadsheet will include essential details such as study characteristics, intervention types, sample sizes, and outcomes related to neurological function, mortality, and the incidence of symptomatic intracerebral hemorrhage (sICH).
Statistical Analysis:
Statistical analyses will be conducted to calculate effect sizes for each outcome. For continuous outcomes, the mean difference in modified Rankin Scale (mRS) scores at 90 days will be computed. For binary outcomes, both the risk ratio and the risk difference will be calculated to compare the incidence of events (e.g., mortality and sICH) between the intervention and control groups. This dual approach will provide a comprehensive understanding of the effectiveness of neuroprotective adjuvants.
Network Meta-Analysis:
Data will be imported into MetaInsight, an online platform specifically designed for conducting network meta-analysis. This will allow for simultaneous comparisons of multiple interventions, synthesizing data from various randomized controlled trials (RCTs). The network meta-analysis will yield estimates of the relative efficacy of different neuroprotective treatments alongside standard reperfusion therapy.
Assessment of Heterogeneity:
Heterogeneity among studies will be evaluated using the I^2 statistic, which quantifies the variability among studies due to factors other than chance. Understanding the level of heterogeneity will help interpret the consistency of the findings across different studies.
Sensitivity Analysis:
Sensitivity analyses will be performed to assess the robustness of the overall findings. This will involve examining the impact of individual studies on the aggregate results to determine if any particular study disproportionately influences the outcomes.
Interpretation and Reporting:

The results will be summarized, highlighting key findings regarding the efficacy of neuroprotective adjuvants in improving functional outcomes and reducing complications in patients with acute

ischemic stroke. Visual representations, such as forest plots and network diagrams, will be generated to enhance clarity in the presentation of results.

Subgroup analysis Subgroup analysis will be conducted to explore the effects of neuroprotective adjuvant treatments in specific patient populations and under varying conditions. This approach will help identify factors that may influence treatment efficacy and provide insights into personalized treatment strategies. The following subgroups will be considered:

Age Groups:
Analysis will be stratified by age (e.g., younger than 65 years, 65 years and older) to determine if treatment effects differ between younger and older patients, who may have varying physiological responses to neuroprotective interventions.
Severity of Stroke:

Patients will be categorized based on the severity of their stroke at presentation, assessed using the National Institutes of Health Stroke Scale (NIHSS). This will help assess whether neuroprotective treatments are more effective in patients with mild versus severe strokes.
Type of Reperfusion Therapy:

Subgroup analyses will differentiate between patients receiving intravenous thrombolysis versus those undergoing intra-arterial thrombectomy. This will allow us to evaluate whether the efficacy of neuroprotective adjuvants varies depending on the type of reperfusion therapy administered.
Specific Neuroprotective Agents:

Analyses will compare the effects of different neuroprotective adjuvants (e.g., cerebrolysin, butylphthalide, hypothermia) within the intervention group to determine if certain agents are more effective than others.
Time to Treatment:

The timing of intervention post-stroke onset will be evaluated, categorizing patients based on whether they received neuroprotective treatments within 3 hours or after 3 hours of symptom onset. This will provide insights into the critical time window for treatment efficacy.
Comorbid Conditions:

Subgroup analysis will also consider the presence of comorbidities (e.g., diabetes, hypertension, atrial fibrillation) to assess their impact on treatment outcomes.
Geographical Variations:

If applicable, the analysis may include geographical differences in treatment response, assessing how regional healthcare practices or patient demographics may influence outcomes.

Sensitivity analysis To enhance the robustness of our study findings, a single sensitivity analysis will be conducted. This analysis will employ a one-study removal method to assess the influence of individual studies on the overall results. Specifically, we will sequentially remove one study at a time from the analysis of the modified Rankin Scale (mRS) scores of 0-2 at 90 days post-reperfusion therapy.
The objective of this sensitivity analysis is to evaluate the consistency of the study conclusions and rankings. By examining the effect estimates after the removal of each individual study, we will determine whether any single study disproportionately affects the overall findings. This approach will help ensure that our conclusions are stable and not overly reliant on any particular study's results.
Through this sensitivity analysis, we aim to validate the robustness of our findings and strengthen the credibility of our conclusions regarding the efficacy of neuroprotective adjuvant treatments in improving functional outcomes following acute ischemic stroke.

Language restriction This review will include studies published in English and Chinese. The decision to restrict the language is based on the need to ensure comprehensibility and accuracy during the data extraction.

Country(ies) involved The study involves authors affiliated with Taiwan, contributing to the research on neuroprotective adjuvant treatments for acute ischemic stroke.

Other relevant information This systematic review and network meta-analysis aims to address the significant clinical challenge posed by acute ischemic stroke (AIS) and the need for effective neuroprotective strategies in conjunction with reperfusion therapies. The following points provide supplementary information relevant to the study:
Clinical Significance:
AIS is a leading cause of mortality and long-term disability worldwide, highlighting the importance of identifying effective adjunctive treatments that can improve functional outcomes for patients. The burden of AIS on healthcare systems necessitates the exploration of neuroprotective interventions that can enhance recovery and reduce complications.
Diversity of Interventions:

The review will evaluate a range of neuroprotective adjuvants, including pharmacological agents and non-pharmacological strategies. This diversity aims to capture the breadth of ongoing research in this field and facilitate a comprehensive understanding of which interventions may be most beneficial when paired with reperfusion therapies.
Interdisciplinary Collaboration:
The research involves collaboration among experts in neurology, emergency medicine, and clinical research methodologies. This interdisciplinary approach enhances the quality of the review and ensures that the findings will be applicable across various clinical settings.
Ethical Considerations:
All studies included in this review are expected to adhere to ethical guidelines governing human research, ensuring that participant welfare and informed consent are prioritized. The review will focus exclusively on studies that have undergone ethical review and approval.
Future Research Directions:
The findings from this review will not only inform clinical practice but also identify gaps in the current literature that warrant further investigation. Potential future studies may focus on exploring the mechanisms of action for various neuroprotective agents and their long-term impacts on stroke recovery.
Limitations:
Potential limitations of this review include variations in study designs, outcome measures, and follow-up durations across included studies. These factors may influence the interpretation of results and the generalizability of findings.
Dissemination of Findings:
The results of this review will be disseminated through publication in a peer-reviewed journal and presentations at relevant conferences. Engaging with the scientific community will ensure that the findings reach clinicians and researchers working in the field of stroke management.

Keywords acute ischemic stroke; reperfusion therapy; thrombolysis; thrombectomy; neuroprotective adjuvant treatments; modified Rankin Scale; mortality; symptomatic intracerebral hemorrhage; randomized controlled trials.

Dissemination plans The findings from this systematic review and network meta-analysis will be disseminated through various strategies to ensure broad reach within the medical and research communities:
Publication in Peer-Reviewed Journals: The primary avenue for dissemination will be to publish the review in a high-impact, peer-reviewed journal focused on neurology or stroke.
Conference Presentations: Results will be presented at relevant national and international conferences to engage with clinicians and researchers, fostering discussions on the implications of the findings.
Workshops and Seminars: We will organize workshops within academic institutions and hospitals to facilitate in-depth discussions on the findings with healthcare professionals involved in stroke management.
Collaborative Networks: Sharing results with professional organizations, such as the American Heart Association, will help integrate findings into clinical guidelines.
Social Media and Online Platforms: Utilizing social media and professional networks will raise awareness among a wider audience, including researchers and the general public.
Patient Engagement: Efforts will be made to communicate findings to patient advocacy groups to educate patients and families about potential benefits.

Contributions of each author

Author 1 - Yi-Hsiang Chen - Author 1 drafted the manuscript, contributed to the study design, performed data analysis, and reviewed the literature. He also assisted in the interpretation of results and ensured the overall quality of the review.
Email: ck951250@gmail.com
Author 2 - Wen-Yi Huang - Author 2 contributed to the development of the selection criteria and performed data validation. She provided writing guidance, assisted in identifying relevant articles for inclusion, and played a key role in synthesizing findings. Additionally, she reviewed and edited the manuscript to enhance its clarity and coherence.
Email: wyh@cgmh.org.tw
Author 3 - Yi-Chia Wei - Author 3 contributed to the development of the study's conceptual framework and provided writing guidance. She performed data validation and assisted in identifying relevant articles for the review. Additionally, she ensured the quality of the manuscript through thorough reviews and revisions.
Email: yichiawei@gmail.com
Author 4 - Meng Lee - Author 4 contributed to the overall study design and methodology, assisted in the network meta-analysis, and provided feedback throughout the writing process. He reviewed the manuscript and approved the final version, ensuring the research adhered to best practices.
Email: menglee5126@gmail.com