Review Article

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Neuroprotective strategies in acute ischemic stroke: A narrative review of recent advances and clinical outcomes

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Abstract:

Reperfusion therapy, which substantially promotes the vessel recanalization rate and improves clinical outcomes, remains the most effective treatment of acute ischemic stroke (AIS). However, a substantial number of patients are either unsuitable for recanalization therapy or experience limited recovery postreperfusion. There is growing recognition that adjunctive neuroprotective therapies may further improve the outcomes in AIS patients by protecting brain tissue during ischemia. Recent advancements in neuroprotective approaches, including pharmacologic agents such as nerinetide edaravone, and uric acid, as well as nonpharmacological interventions, such as remote ischemic conditioning and normobaric hyperoxia, offer promising potentials in stroke care. This review provides an overview of the current neuroprotective therapies, examines recent clinical evidence, and discusses the strengths and weaknesses of certain clinical trials aimed at cerebral protection.

Keywords:

Acute ischemic stroke, cerebral protection, clinical study, reperfusion therapy

Introduction

Acute ischemic stroke (AIS) results from the occlusion of a cerebral artery, leading to reduced blood flow to a certain area of the brain. Over the past several decades, recanalization therapy, including intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT), has demonstrated considerable efficacy in reopening cerebral arteries and improving functional outcomes in patients with AIS.[1-3] Although IVT is widely accessible for AIS patients, its therapeutic window is limited to 4.5–6 h and is less effective for large artery occlusions, achieving recanalization in fewer than 20% of such cases.[4] In contrast, EVT can achieve a recanalization rate of up to 80% in patients in large vessel occlusions (LVOs), but <50% of patients achieve functional independence, and more than 15% of patients die.[5-8] Cerebral protective strategies could offer potential as an adjunctive treatment to address the limitations of recanalization therapies, potentially improving reperfusion efficacy. In recent years, extensive research has been dedicated to the development of cerebral protection therapies aimed at protecting the brain from damage after stroke.[9,10] Although many neuroprotective methods have shown significant benefits in improving the outcomes in animal models of stroke, their efficacy has often failed to translate into human clinical trials. This review provides an overview of the recent advancements in clinical trials of current and promising neuroprotective treatment for stroke [Table 1] and explores the challenges hindering successful clinical translation.

Targeting Neuronal Excitotoxicity

Following a stroke, glutamate, an excitotoxic neurotransmitter, is released into the synaptic gap, causing overstimulation of neuronal receptors, which leads to ischemia and cell death. In recent years, numerous strategies have been developed to mitigate glutamate-mediated excitotoxicity in AIS.[25]

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Table 1: Clinical trials of cerebral protection for acute ischemic stroke

Study	Study design	Patients	Intervention	Primary outcome	Findings
Fladt *et al*., 2024[11]	Multicenter, randomized, double-blinded, placebo-controlled trial (REPERFUSE-NA1 Trial), *n*=71, 7 sites in Canada and the United States	Age ≥18 years; stroke (NIHSS >5) within 12 h of onset and underwent EVT; ASPECTS of ≥5; moderate-to-good collateral circulation; proximal occlusion in the intracranial internal carotid artery or the M1 segment of the MCA	NA-1 or a saline placebo after EVT	The DWI infarct growth early after EVT between sequential MRI <5 h post-EVT and at 24 h	Patients receiving NA-1 showed a median early secondary infarct growth of 5.92 mL compared with 10.80 mL in patients with a placebo (*P*=0.30)
Hill *et al*., 2020[12]	Multicentre, double-blind, randomized, placebo-controlled study (ESCAPE-NA1 Trial), *n*=1105, sites in eight countries	Age ≥18 years; AIS (NIHSS >5) within 12 h of onset and due to proximal intracranial internal artery occlusion; ASPECTS >4; moderate-to-good collateral filling	NA-1 in a single dose of 2.6 mg/kg or placebo after EVT	The mRS score of 0–2 at 90 days	61.4% of patients with NA-1 and 59.2% of patients with placebo achieved an mRS score of 0–2 at 90 days (*P*=0.35)
Chabriat *et al*., 2020[13]	Randomized, double-blind, parallel-group, placebo-controlled, multicentre phase 2 trial (RESTORE BRAIN Trial), *n*=585, 92 sites in 14 countries	18–85 years of age; AIS (NIHSS 7–20) between 2 days and 6 days of onset; without previous disability	150 mg S44819 twice a day, 300 mg S44819 twice a day, or placebo twice a day for 90 days	mRS score at 90 days from onset of randomization	mRS at day 90 did not differ among the three groups. The median NIHSS score, the median MoCA score, and the Barthel index were similar in all groups. The number and type of adverse events were similar among groups
Wu *et al*., 2023[14]	Multicenter, double-blind, placebo-controlled randomized clinical trial, *n*=3072, 67 sites in China	18–75 years of age; AIS (NIHSS 4–15) within 14 days of onset	120 mg Xuesaitong soft capsules orally twice daily or placebo for 3 months	Proportion of mRS 0–2	89.3% of patients in the Xuesaitong group and 82.4% of patients in the control group achieved mRS 0–2 at 3 months (*P*<0.001)
Bladin *et al*., 2023[15]	Multicenter, phase 2 prospective randomized clinical trial (TEXAIS Trial), *n*=350, 12 sites in Australia, New Zealand, and Finland	Age ≥18 years; AIS within 9 h of onset; blood glucose level ≥4 mmol/L; prestroke mRS score of ≤2	5 μg exenatide subcutaneous injection twice daily or standard care for 5 days	The proportion of patients with ≥8-point improvement in NIHSS scores or NIHSS scores 0–1 at 7 days poststroke	No differences in primary outcome were observed in the two groups. The per-patient mean daily frequency of hyperglycemia was significantly less in the exenatide group
Xu *et al*., 2021[16]	Multicenter, randomized, double-blind, comparative, phase III clinical trial (TASTE Trial), *n*=1165, 48 sites in China	AIS (NIHSS 4–24) within ages 35–80 years; AIS (NIHSS 4–24) within 48 h of onset; a total score of upper and lower limbs on motor deficits ≥2 at admission	Edaravone dexborneol (edaravone, 30 mg; (+)-borneol, 7.5 mg) or edaravone (30 mg), injection once every 12 h, and continued for 14 days	The proportion of patients with mRS score ≤1 on day 90	The edaravone dexborneol group showed a significantly higher proportion of patients experiencing mRS ≤1 (*P*=0.004)
Zhang *et al*., 2023[17]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, *n*=3448, 100 sites in China	Aged 18–80 years; AIS (NIHSS 4–24) within 48 h of onset and an upper and lower limb motor deficit score on the NIHSS of at least 2	25 mg GDLM or placebo once daily and continued for 14 days	The proportion of patients with the mRS of 0 or 1 at 90 days	Significant differences in primary outcome were observed in the two groups (*P*<0.001)
Bang *et al*., 2022[18]	Investigator-initiated, prospective, randomized, open-label, controlled trial with blinded outcome evaluation, *n*=54, 4 sites in Korea	Aged 30–75 years; chronic major stroke (NIHSS 6–21) within 90 days of onset	Participants were assigned a 2:1 ratio to receive autologous MSC IV or standard treatment	Circulating factors that are associated with the clinical improvement in the Fugl-Meyer Assessment and neuroplasticity on diffusion tensor image and resting-state functional MRI	Circulating EV levels were increased about 5-fold within 24 h after injection of MSCs (*P*=0.001). EV number was independently associated with improvement in motor function. Integrity of the ipsilesional corticospinal tract and intrahemispheric motor network were significantly correlated with circulating EV levels, respectively (*P*<0.05)

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Table 1: Contd...

Study	Study design	Patients	Intervention	Primary outcome	Findings
Chung *et al*., 2021[19]	Prospective, open-label, randomized controlled trial with blinded outcome evaluation (STARTING-2 Trial), *n*=39, 7 sites in Canada and the United States	Aged 30–75 years; severe MCA territory infarct (NIHSS 6–21) within 90 days of symptom onset	Participants were assigned, in a 2:1 ratio, to receive IV MSC injections or standard care alone	The score on mRS at 3 months	There was no significant difference between the groups in the mRS score at 3 months (*P*=0.732). Significant improvements in lower extremity motor function in the MSC group compared to the control group (*P*=0.023)
van den Berg *et al*., 2022[20]	Investigator-initiated, phase 3, multicentre, ambulance-based, randomized trial with open-label treatment and blinded endpoint assessment (MR ASAP Trial), *n*=325, 18 sites in the Netherlands	Aged ≥18 years; probable acute stroke; a face-arm-speech-time test score of 2 or 3; systolic blood pressure of at least 140 mmHg; started treatment within 3 h of onset	Transdermal glyceryl trinitrate 5 mg/day of onset for 24 h plus standard care or to standard care alone	The functional outcome was assessed with the mRS at 90 days	In the total population (*n*=325), the median mRS score at 90 days was 2 (IQR 1–4) in both two groups (adjusted common OR 0.97 [95% CI 0.65–1.47]). In patients with diagnosed stroke (*n*=291), the 90-day mRS score was 2 in the glyceryl trinitrate group versus 3 in the control group (0.92 [0.59–1.43]). In patients with intracerebral hemorrhage, 34% of patients allocated to glyceryl trinitrate versus 10% allocated to the control group died within 7 days (adjusted OR 5·91 [0·78–44·81]); death within 90 days occurred in 46% in the glyceryl trinitrate group and 55% in the control group (adjusted OR 0·87 [0·18–4·17])
Hankey *et al*., 2020[21]	Randomized, parallel-group, double-blind, placebo-controlled trial (AFFINITY Trial), *n*=1280, sites in Australia, New Zealand, and Vietnam	Age ≥18 years; stroke within 2–15 days of onset and persisting neurological deficit	Fluoxetine 20 mg or matching placebo orally once daily for 6 months	The mRS distribution at 6 months	The distribution across mRS categories at 6 months was similar in the fluoxetine and placebo groups (*P*=0.53). Fluoxetine increases the risk of falls, bone fractures, and epileptic seizures
Lundström *et al*., 2020[22]	Multicentre, randomized, placebo-controlled, double-blind, parallel-group trial (EFFECTS Trial), *n*=1500, 35 sites in Sweden	Age ≥18 years; stroke within 2–15 days of onset and persisting neurological deficit	Fluoxetine 20 mg or matching placebo orally once daily for 6 months	The mRS distribution at 6 months	The distribution across mRS categories at 6 months was similar in the fluoxetine and placebo groups (*P*=0.42). Fluoxetine reduced the occurrence of depression but increased the risk of bone fractures and hyponatremia
Dennis *et al*., 2019[23]	Multicentre, parallel-group, double-blind, randomized, placebo-controlled trial (FOCUS Trial), *n*=3127, 103 sites in the UK	Age ≥18 years; patients with stroke between 2 and 15 days of onset and persisting neurological deficit	Fluoxetine 20 mg or placebo orally once daily for 6 months	The mRS distribution at 6 months	The distribution across mRS categories at 6 months was similar in the fluoxetine and placebo groups (*P*=0.439). Fluoxetine prevented the occurrence of depression after stroke but increased the frequency of bone fractures
Pruvost-Robieux *et al*., 2021[24]	Pilot single-center, prospective double-blind, and sham-controlled clinical phase IIa trial (STICA Trial), *n*=45, 1 site in France	>18 years of age; AIS in the MCA territory (NIHSS 4–25) and eligible for IVT	A current of 1.5 mA or sham current was delivered for 20-min epochs, delivered every hour over 6 h and 20 min	24-h infarct growth between admission and 24 h after initiation of reperfusion therapy	There was no significant difference between the groups for any end-point

EVT: Endovascular thrombectomy, MCA: Middle cerebral artery, MRI: Magnetic resonance imaging, mRS: Modified Rankin Scale, AIS: Acute ischemic stroke, GDLM: Ginkgo diterpene lactone meglumine, MSCs: Mesenchymal stem cells, EV: Extracellular vesicle, IV: Intravenous, IQR: Interquartile range, OR: Odds ratio, CI: Confidence interval, IVT: IV thrombolysis, NA-1: Nerinetide, DWI: Diffusion-weighted imaging

These approaches focus on reducing glutamate release, antagonizing glutamate receptors, and enhancing glutamate uptake. While preclinical studies have shown promising results, translating these findings from bench to bedside remains a challenge.[26-28]

Nerinetide (NA-1) is a promising neuroprotective agent that targets excitotoxic pathways through NMDA receptor inhibition. Preclinical studies have demonstrated its ability to reduce infarct volumes and improve recovery, but clinical trials have yielded mixed results.[29-31] In the

ESCAPE-NA1 Phase III trial, NA-1 did not improve the functional outcomes when used with EVT and the clot-dissolving drug alteplase. In patients who received NA-1 with EVT alone (without alteplase), there was a trend toward better recovery in disability outcomes, suggesting that alteplase may interfere with NA-1's effectiveness.[12] A similar trend was observed in the REPERFUSE-NA1 trial, further indicating that concurrent alteplase treatment may modify NA-1's effects.[11] Future research designs should further substantiate the potential interactions between NA-1 and alteplase and identify patients who would benefit from NA-1 and other neuroprotective agents.

S44819, a selective antagonist of the $GABA_A$ α5 receptor, aimed to promote neuroplasticity by modulating neuronal inhibition in ischemic regions. Preclinical studies showed that the administration of S44819 after stroke reduced neuronal injury and increased neuroplasticity.[32,33] However, the Phase II RESTORE BRAIN trial, which administered S44819 to stroke patients within 2–6 days of stroke onset, failed to demonstrate significant improvement in functional recovery 3 months poststroke as measured by the modified Rankin Scale (mRS). Several factors may have contributed to these negative results. The efficacy of S44819 could have been overestimated based on studies conducted on young, healthy male animals. In addition, the mRS primarily assesses motor performance and may fully capture nonmotor aspects of recovery, such as language abilities or psychosocial variables.[13]

Targeting Oxidative and Nitrosative Damage

Following excitotoxic ischemic injury, oxidative and nitrosative stress are triggered by the overproduction of free radicals, which leads to inflammation, immune cell aggregation, and, finally, neuronal death.[34] Neutralizing oxidative and nitrosative stress has been explored as a promising neuroprotective strategy.

Edaravone dexborneol, a novel neuroprotective agent combining antioxidant and anti-inflammatory effects, has shown the potential to improve the stroke outcomes. A Phase III multicenter trial found that edaravone dexborneol, compared to edaravone alone, improved the proportion of patients who achieved good functional outcomes after 90 days, defined by a mRS score of 1 or less.[16] This suggests that using a multitarget approach may be more effective than single-pathway treatments. Notably, this trial lacked a placebo control group and did not include patients undergoing recanalization therapies. In the TASTE-2 (NCT05249920) Phase III trial, 1,105 patients diagnosed with anterior circulation AIS due to LVO were randomized to receive edaravone dexborneol or a placebo before EVT. The results demonstrated improved functional recovery in those treated with edaravone dexborneol before EVT, suggesting that pretreatment with neuroprotective agents could enhance the efficacy of EVT in LVO strokes.

Regarding glucose management poststroke, hyperglycemia-induced oxidative stress is a concerning complication.[35] Insulin-based trials aimed to control the glucose levels have not resulted in clinical benefits.[36,37] In contrast, Glucagon-like peptide-1 receptor agonists, such as exenatide, which stimulates the release of insulin and suppresses glucagon in a glucose-dependent manner, have shown promise to reduce the likelihood of hypoglycemia risk.[38] Preclinical studies indicate that exenatide reduces oxidative stress and infarct volume.[39] However, this did not translate to clinical trials. In a Phase II trial, the use of exenatide did not result in significant neurological improvement, as measured by the NIHSS score at 7 days poststroke. These findings indicate a need for larger-scale studies to explore its potential benefits.[15]

Panax notoginseng saponins, traditionally used in Chinese medicine, exhibit anti-inflammatory, antioxidant, and pro-angiogenic properties.[40-43] Xuesaitong soft capsules, derived from *Panax notoginseng*, reported positive outcomes in rodent models by reducing infarct volume and neurologic impairment.[44] Moreover, a clinical trial involving over 3,000 AIS patients demonstrated that Xuesaitong soft capsules improved functional outcomes at 3 months. The study population had moderate baseline stroke severity, and patients did not receive recanalization therapies, suggesting the need for further research to assess the benefit of combining these agents with standard reperfusion therapies.[14]

Similarly, Ginkgo diterpene lactone meglumine (GDLM), another compound derived from traditional Chinese medicine, targets oxidative stress, inflammation, and apoptosis.[45-47] In a multicenter clinical trial, patients within 48 h of stroke onset were randomly assigned to receive GDLM or a placebo. Results showed improved functional outcomes at 3 months in the GDLM group. While promising, these trials did not include patients who received intravenous thrombolysis or mechanical thrombectomy, highlighting a gap in understanding its potential as an adjunct to reperfusion therapies.[17]

Mesenchymal Stem Cells Therapy

Mesenchymal stem cell (MSC) therapy has emerged as a potential neuroprotective strategy for patients with AIS due to its ability to secrete biofactors, such as cytokines, chemokines, extracellular vesicles (EVs), and trophic factors that promote tissue repair. Clinical trials investigating MSC therapy in stroke have shown mixed results, further highlighting the challenges of translating preclinical success into favorable clinical outcomes.[19,48-50]

For example, the STARTING-2 trial, which assessed the impact of MSC injections on chronic stroke recovery, found no significant differences in functional outcomes between the MSC-treated group and placebo after 90 days, as measured by the mRS. The secondary analyses suggested potential benefits in lower extremity motor function. This discrepancy may be attributed to the mRS's limited sensitivity in detecting subtle improvements in motor recovery.[19]

In addition, a trial by Bang *et al*. explored the efficacy of bioactive substances secreted by MSCs in stroke recovery. In this study, patients with chronic major stroke were randomized to receive either intravenous autologous MSCs or standard treatment (acute stroke management protocols without MSC therapy). The results suggest that higher levels of EVs were associated with improved motor function and neuronal plasticity detected by magnetic resonance imaging at 3 months. However, there was variability in EV levels among patients despite receiving the same MSC dose, raising questions about the source of these EVs, as they can originate from various cells, such as blood cells and endothelial tissues.[18] Further research is needed to mark the MSC-derived EVs using various tagging strategies.

Other Neuroprotective Methods

The MR ASAP (ISRCTN99503308) was a Phase III trial investigating the efficacy of prehospital glyceryl trinitrate, a vasodilator, for patients with presumed acute stroke. However, the trial was prematurely halted due to safety concerns in patients with intracerebral hemorrhage. The primary outcome, measured by the mRS score at 90 days, showed no significant differences between the treatment and control groups, including subgroups of patients with ischemic stroke or hemorrhage. Moreover, there was no benefit from giving glyceryl trinitrate within 3 h of stroke onset, and it was suggested that early use in patients with hemorrhage might even increase mortality risk.[20]

Fluoxetine, a selective serotonin-reuptake inhibitor, demonstrated similar mixed clinical outcomes.[51,52] Trials across multiple countries showed that daily fluoxetine use in stroke patients did not significantly improve the patient outcomes when comparing their mRS score to the control group.[21-23] Fluoxetine did decrease the likelihood of developing depression poststroke, but was linked to complications such as increased bone fractures, falls, epileptic seizures, and hyponatremia, leading researchers to conclude that the risks outweigh using this therapy for stroke.

Finally, cathodal transcranial direct current stimulation (C-tDCS) is a noninvasive neurostimulation technique that modulates neuronal excitability through the application of low-powered electrical currents to the scalp. The STICA (cathodal transcranial direct stimulation in acute middle cerebral artery stroke) assessed the safety, feasibility, and efficacy of patients with AIS eligible for reperfusion therapies. Participants received 20-min stimulation sessions every hour for a total of 6 h. Preliminary results indicate that C-tDCS was both safe and feasible, with minor side effects of itching or burning sensations at the electrode site. However, due to the small sample size, results could have been influenced by a chance bias due to imbalances between groups, warranting further studies with larger sample populations to confirm these findings.[24]

Reasons for Failure of Clinical Trials

A wide range of cerebral protection agents has demonstrated efficacy in reducing infarct growth and improving functional outcomes in animal models. However, most of these agents have shown limited success when translated into clinical trials. One key issue is the heterogeneity of stroke presentations in patients is not adequately replicated in animal models. Stroke patients frequently present with multiple comorbidities, such as hypertension, diabetes, hyperlipidemia, thrombus, and atrial fibrillation, all of which contribute to the process of vascular injury.[53,54] However, preclinical studies typically select male and healthy animals, potentially weakening the strength or validity of the trials.

Historically, trials of neuroprotection have focused on single-target pathophysiological mechanisms of stroke, such as excitotoxicity and oxidative damage. However, it is not sufficient to yield meaningful improved clinical outcomes. In addition, the delayed timing of drug administration in clinical settings often occurs after the peak stage of the pathological processes, which may diminish the effectiveness of neuroprotective intervention.

Another limitation is that most clinical trials have enrolled patients without concomitant thrombolysis or thrombectomy, overlooking the interactive influence between the protect agent and reperfusion therapy. Moreover, for safety concerns, clinical trials of neuroprotection typically selected a lower dose, which may further reduce their effectiveness.

Finally, many studies have relied on mRS as the primary measure of functional outcomes.[55] While the mRS score may be useful to assess the broad categories of disability and independence, it may lack the sensitivity to detect subtle changes in motor function. This limitation is evident in studies where primary analyses showed no significant differences and where secondary analyses suggested improvements in motor function that were not

reflected by mRS scores. It is noteworthy that the lack of significant improvement in mRS scores may indicate that the neuroprotective agents are insufficiently effective in enhancing stroke prognosis.

Conclusion

Despite numerous clinical translation failures for neuroprotective treatment in recent years, which has reduced expectations, the advancements and widespread application of recanalization therapies have renewed optimism in the field. Promising results have been reported with agents such as uric acid, edaravone dexborneol, and Xuesaitong soft capsules. Future efforts should focus on expanding the use of neuroprotective strategies as adjunctive treatment in combination with recanalization. However, it is important to mitigate the adverse interactions between the treatments, especially those between cerebral protective drugs and thrombolysis.

Given the heterogeneity of stroke in patients, preclinical studies should incorporate animal models that have comorbidities to better reflect the broader patient population, potentially increasing the validity of these studies. Given the substantial proportion of ischemic stroke linked to atherosclerosis and the challenges associated with establishing preclinical models, animal models featuring hyperlipidemia may be prioritized for initial preclinical studies. In addition, novel neuroprotective drugs should aim to target multiple aspects of the ischemic cascade. Considering the early onset of certain pathophysiological processes in AIS, initiating neuroprotective treatments in prehospital settings could be a promising strategy to extend the benefits of these agents to a larger patient population.

Author contributions

All authors were responsible for the conception and design of the study. Conceptualization, W.Z.; writing—original draft preparation, M.Z.; writing—review and editing, Y.Q.; revision, A.W.; review and funding acquisition, W.Z. All authors have read and agreed to the published version of this manuscript.

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Not applicable.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest

Wenbo Zhao is an Associate Editor of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of the Editor and their research groups.

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