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Invited Review

Current neuroprotective agents in stroke

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ABSTRACT

What is expected from neuroprotection is to inhibit neuronal death and halt or decelerate the neuronal loss to lower the mortality rates, decrease disability, and improve the quality of life following an acute ischemic stroke. Several agents were described as neuroprotective up to date; however, there is still debate which to use in the neurorehabilitation of stroke patients, in terms of both efficacy and also safety. In this review, we discuss the agents, citicoline, cerebrolysin and MLC901 (NeuroAiD II), the three agents which have started to be used frequently in neurorehabilitation clinics recently in the light of the current literature.

Keywords: Cerebrolysin, citicoline, MLC901 (NeuroAiD II), neuroprotective, stroke.

Stroke continues to pose a significant health concern, affecting millions of individuals globally, a common cause of mortality and significant contributor to disability in survivors. Early interventions for the occluded artery system are essential in the management of ischemic stroke. Literature regarding neuroprotection often mentions "Time is Brain," emphasizing the fact that 2 million neurons die every minute following an ischemic stroke, if no effective therapy is applied.[1] The number of patients meeting the criteria for recanalization therapies such as thrombolysis and mechanical thrombectomy is still limited; therefore, the need for various therapeutic approaches has emerged, aiming to intervene in the pathophysiological cascade initiated by ischemia, ultimately preventing irreversible tissue damage. Neuroprotective agents have garnered increased interest in recent years.[2]

There is remarkable debate about the neurotrophic medications in acute ischemic stroke (AIS). However, neuroprotective agents are commonly used as supplementary therapy for AIS in clinical practice.[3] A recent comprehensive examination and analysis of registered pharmacological treatments aimed at enhancing neurorecovery following a stroke has been released. The agents are listed in Table 1.[4]

This review consists of not all these agents, but includes citicoline, cerebrolysin and MLC901 (NeuroAiD II), which are increasingly utilized in acute or subacute stroke patients within neurology and rehabilitation clinics.

CITICOLINE

Phospholipids are part of the cell membrane structures managing physiological functions,[5] playing a role in both humoral immunity and also nerve impulse conduction and neurotransmission in the neuronal cell membrane. The four types of phospholipids are phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine and sphingomyelin.[6]

Phosphatidylcholine is important for neuronal growth and regeneration. Citicoline, also known as cytidine-5'-diphosphocholine (CDP-choline), mirrors the natural intracellular precursor of phosphatidylcholine.[7] Administering CDP-choline offers an external supply of both cytidine and choline. Choline plays a role in neurochemical processes. Cytidine is used for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis,[8] among several other functions. Following cerebral ischemia,

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TABLE 1
Neuroprotective agents[4]

Category	Agents
Antidepressants	Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, maprotiline, nortriptyline
Botanicals	Di huang yin zi, ginkgo biloba, panax notoginseng, MLC601/MLC901
Calcium antagonists	Nimodipine, flunarizine, isradipine, nicardipine, fasudil, lifarizine
Minerals	Magnesium
Choline nucleotides	Citicoline
Cholinergics	Donepezil, rivastigmine, galantamine
Central nervous system stimulants	Amantadine, modafinil, amphetamine, methylphenidate
Colony stimulating factors	EPO, GCSF
Dopaminergics	Levodopa, ropinirole, bromocriptine, pergolide, pramipexole, carbidopa/levodopa, amantadine
Ergots	Hydergine
Gamma-aminobutyric acid (GABA) agonists	Clomethiazole, diazepam
Methylxanthines	Aminophylline, pentoxifylline, propentofylline, theophylline
Monoamine oxidase (MAO) inhibitors	Moclobemide, selegiline
Mood stabilizers	Lithium
Neuropeptides	Cerebrolysin
N-Methyl-D-aspartate (NMDA) agonists	Cycloserine
NMDA antagonists	Memantine
Norepinephrine/noradrenergics	Atomoxetine, reboxetine
Opioid antagonists	Naloxone, nalmefene
Peripheral chemoreceptor agonists	Almitrine-raubasine
Potassium channel blockers	Dalfampridine
Pyrazolones	Edaravone
Racetams	Piracetam
Vasodilators	Buflomedil, cinepazide

EPO: Erythropoietin; GCSF: Granulocyte-colony stimulating factor.

endogenous synthesis of CDP-choline is hindered due to the cell's deficiency in high-energy phosphates. To restore the neuronal activity after cerebral ischemia, the demand for drugs that can enhance the production of structural phospholipids in cell membranes has emerged, prompting investigation into citicoline administration in cerebral ischemia.

Citicoline has been examined by *in vitro* studies of cerebral ischemia via the intraperitoneal route in rats, dogs, cats, guinea pigs, gerbils, mice, etc., subjected to hypoxia. Studies have suggested that citicoline decreases blood-brain barrier leakage after ischemia in gerbils and reduces the volume of cerebral edema significantly.[9] Additionally, citicoline shows promise in restoring dopamine turnover in ischemic brain tissue in rats and appears to improve experimental cerebral ischemia.[10] It enhances metabolic activity in the brain during ischemia,[11] increases neuronal plasticity,[12] and has a beneficial impact in relation to spatial cognition and memory in rats following focal cerebral ischemia.[13] The experimental study of citicoline in rats due to cerebral ischemia showed a prolonged onset of stroke and arrest.[14] Schäbitz et al.[15] investigated rats with cerebral ischemia using both low-dose and high-dose citicoline and a placebo, finding no significant differences in neurological assessment among all groups. However, the mean infarction volume was statistically lower in the high-dose group, and the volume of cerebral edema was also lower in the high-dose group, although it was not statistically significant. In certain studies, citicoline demonstrated synergistic efficacy when combined with other medications for treating cerebral ischemia, such

as thrombolytics or neuroprotective drugs. Higher doses of citicoline and a combined usage of lower doses of citicoline with recombinant tissue plasminogen activator (r-tPA) notably diminished the extent of brain infarctions.[16] Mice intracerebral hemorrhage model, animals treated with citicoline exhibited no variance in hematoma volumes but displayed a notable decrease in surrounding ischemic damage, suggesting a potential therapeutic role for citicoline in intracerebral hemorrhage.[17]

Clinical studies on citicoline in cerebral ischemic patients present conflicting results. Some favorable studies indicate that citicoline increases long-term functional independence.[6,18] A systematic review emphasizes a significant improvement in functional outcomes with citicoline in AIS patients,[19] consistent with other studies showing efficacy in functional outcomes,[20,21] as well as improvement in motor function.[22] Early administration of citicoline is recommended for patients unsuitable for reperfusion therapies.[23] In a randomized clinical trial administering citicoline to acute stroke patients, both hemorrhagic and ischemic, the citicoline group showed statistically significant lower disease severity than the control group after Day 90, particularly in ischemic patients,[24] prompting long-term citicoline administration.

A meta-analysis revealed significant long-term functional outcome improvement with neuroprotectants such as cerebrolysin, citicoline, MLC601 (NeuroAiD) and edaravone, compared to placebo in AIS, advocating for the use of neuroprotective agents in patients ineligible for thrombolysis or thrombectomy.[25] The ICTUS trial,[26] a large, randomized, placebo-controlled, sequential trial on citicoline, was conducted in Europe. Acute ischemic stroke patients were randomly assigned to either citicoline or placebo, with a drug protocol including intravenous citicoline administration for the first three days followed by oral administration for six weeks. Evaluation parameters were the National Institutes of Health Stroke Scale (NIHSS), and also modified Rankin Scale (mRS), as well as Barthel Index (BI). At the end, both the citicoline and placebo groups demonstrated similar recovery rates, with comparable safety parameters and rates of adverse events in the ICTUS trial. The trial concluded that citicoline did not show effect in moderate-to-severe AIS cases. However, Overgaard[27] later suggested a possible beneficial effect of citicoline compared to placebo, particularly in patients not treated with r-tPA, those aged over 70 years, and those with less severe stroke (NIHSS score <14), with a safety profile similar to placebo.

Nevertheless, some studies or meta-analyses have found citicoline to be ineffective in acute stroke patients. For instance, the CAISR (Citicoline in Acute Ischemic Stroke Research) study, a single-center, randomized, placebo-controlled, parallel-group trial, compared citicoline with placebo early after recanalization therapy and two groups showed no significant difference.[28] Meta-analyses[29,30] did not support the effectiveness of citicoline in acute stroke patients, and a Cochrane review[31] suggested little to no difference between placebo and citicoline.

CEREBROLYSIN

Cerebrolysin is a mixture of neuropeptides that has similar properties to neurotrophic factors, a peptidergic medication consisting of low molecular weight porcine-derived peptides (25%) and free amino acids (75%).[32,33]

Rehabilitation following a stroke necessitates a multifaceted approach, encompassing cognitive and motor rehabilitation, as well as pharmacological intervention, some authors offering cerebrolysin the first choice for pharmacological supports.[34]

Wan et al.,[3] after their research of the meta-analyses and systematic review of cerebrolysin in AIS, reported that cerebrolysin improved neurological function, aided in daily activities, lowered blood viscosity and fibrinogen levels, and ultimately led to better patient outcomes. The safety profile of cerebrolysin was found to be similar to the controls.

In Cerebrolysin and Recovery After Stroke (CARS) trial, cerebrolysin therapy after stroke was assessed. It was a prospective, randomized, double-blind, placebo-controlled, multi-center study, comparing 30 mL cerebrolysin 20 min intravenous infusion once daily for 21 days, versus placebo, beginning at 24 to 72 h after stroke onset, in early rehabilitation after stroke. The patients were evaluated in terms of upper limb motor function, gait velocity, fine motor function, aphasia, neglect, depression, disability, dependence in activities of daily living, quality of life and global neurological state, from baseline to day 90. The CARS trial demonstrated significantly positive effects of cerebrolysin comparing to placebo on upper limb motor function and global outcome after 90 days, providing evidence of efficacy in stroke.[35]

A recent *in vitro* study investigated the neuroprotective effects of both cerebrolysin and citicoline.[36] The study assessed the efficacy of these drugs in promoting the recovery of cultured neurons during the reperfusion period following oxidative stress. The injury group exhibited higher expressions of neuregulin 1 (NRG1) and brain-derived neurotrophic factor (BDNF) compared to the control group, indicating the neuronal defense mechanisms to injury. The NRG-1 plays a role in myelination and has a significant impact on the recovery phase after ischemic events like stroke. The BDNF is crucial for neuronal repair, survival, differentiation, and synaptic function. Cerebrolysin significantly increased the expression of both NRG1 and BDNF genes. Citicoline, on the other hand, notably enhanced the expression of the BDNF gene, but did not show a significant elevation in NRG-1 expression. The substantial increase in BDNF gene expression observed with both citicoline and cerebrolysin suggests the potential involvement of growth factor-mediated mechanisms in rescuing oxidatively stressed cells. The research findings indicated that both citicoline and cerebrolysin exhibited a small but significant protective effect on Neuro-2A cells following oxidative damage, enhancing their survival. The two drugs suggested similar neuroprotective effects.

Cerebrolysin was recommended for the paretic upper limb after stroke in the 2020 revised guideline of the German Society of Neurorehabilitation. The recommendation entails administering cerebrolysin during the acute and subacute phases of stroke in patients exhibiting upper limb motor deficits. Preferably, this administration should occur within the first 24 to 72 h post-stroke, intravenously, on a daily basis for 21 days, alongside a tailored rehabilitation program aimed at enhancing motor function of the upper extremities and overall functional condition.[37]

The European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after AIS, published in 2021,[38] highlights cerebrolysin's significant effects compared to standard care. At one month after stroke, cerebrolysin demonstrated beneficial and statistically significant effects on early motor performance and neurological function using the Action Research Arm Test (ARAT) and NIHSS scales, respectively. At three months, while still beneficial, the effects were not statistically significant. Similarly, for global functional outcome measured by mRS, cerebrolysin showed significant improvement at both one and three months after stroke compared to standard care. Safety profile was similar in both groups. Based on evidence quality, a weak recommendation for cerebrolysin (30 mL/day, intravenous, minimum 10 days) is provided for early motor neurorehabilitation after moderate to severe ischemic stroke. The Stroke Rehabilitation Clinician Handbook recommends a regimen of cerebrolysin, daily intravenous administration for three weeks, accompanied by physical therapy to improve motor function of the upper extremity.[2,39]

A systematic review and meta-analysis of 12 randomized-controlled trials conducted in 2021 assessed the safety of cerebrolysin following stroke. No statistically significant differences between cerebrolysin and placebo in terms of adverse events, serious adverse events, non-fatal serious adverse events, and death, indicating a favorable safety profile for cerebrolysin were detected.[40]

While the role of cerebrolysin in ischemia has been broadly researched, its effect in subarachnoid hemorrhage (SAH) remains relatively unexplored. A recent meta-analysis of available clinical trials evaluating cerebrolysin's effect in SAH suggested positive outcomes, particularly in reducing mortality rates. Although the study showed a potential positive influence on the length of stay for SAH patients, the limitation of insufficient data prevents analysis of cerebrolysin's effect on the Glasgow Outcome Score. Further randomized clinical trials with larger patient cohorts are recommended.[41] In 2022, the Clinical Practice Guideline for Stroke Rehabilitation in Korea recommended cerebrolysin for improving motor function, with very low evidence level and conditional recommendation (level B) for stroke patients, depending on individual patient condition and risk of side effects.[42]

NEUROAID

NeuroAiD MLC601 and NeuroAiD II MLC901 are Traditional Chinese Medicine (TCM) formulations with a history of over 2,500 years. They are combinations of herbal and animal components. The MLC601 contains nine herbal components (including Radix astragali, Radix paeoniae rubra, Radix salviae miltiorrhizae, Radix angelicae sinensis, Rhizoma chuanxiong, Prunus persica, Carthamus tinctorius, Radix polygalae, Rhizoma acori tatarinowii) with five animal components (including Hirudo, Calculus bovisartifactus, Eupolyphaga seu steleophaga, Cornu saigae tataricae and Buthus martensii). Conversely, MLC901 comprises solely nine herbal components.

Heurteaux et al.'s[43] study demonstrated several beneficial effects of these formulations:

- Protection of cortical neurons against aging-associated death in culture.
- Protection against glutamate-induced cell death in cortical cultures.
- Pre- stroke and post-stroke administration of MLC601 and MLC901 protect against ischemic brain injury *in vivo*.
- Pre-treatment with MLC901 protects against functional deficits induced by focal ischemia *in vivo*.
- Treatment with MLC601 and MLC901 stimulates neurogenesis, neurite outgrowth and proliferation.

The MLC901 enhances animal survival rates and fosters the restoration of neurological function, as well as decreases neurodegeneration, with no changes on physiological factors. Both MLC601 and MLC901 protect the brain against ischemia, with oral pre- and intraperitoneal post-treatment leading to decreased mortality and infarct volume. The MLC901 also restores damaged neurons and neuronal circuits, resulting in behavioral benefits. The MLC901 increases BDNF *in vitro*, which induces anti-apoptotic mechanisms, reduces infarct volume and decreases secondary cell death.[44]

Radix astragali, the main herbal ingredient of MLC601 and MLC901, is associated with scavenging active oxidants, regulating cytokine expression, and nitric oxide production.[45] Following *in vivo* injury and middle cerebral artery occlusion in mice for 1 h, MLC901 administered at 90 min. Administration of MLC901 led to a decrease in infarct volume, reduction in blood-brain barrier permeability and brain edema, enhancement in neurological assessments, and a decrease in reported mortality rates within 24 h.[46]

In the CHIMES study (1,100 patients randomized in a placebo-controlled, double-blind, multi-center study, in which medication started in 72 h and followed up for three months), no statistically significant difference was detected in mRS at three months. However, in the subgroup where medication started before 48 h, benefits were noted. Serious and non-serious adverse effects were similar.[47] The six-month follow-up in the CHIMES study did not show statistically significant differences. In the CHIMES extension study (CHIMES-E), the likelihood of achieving functional independence, defined as an mRS score of ≤1, markedly improved at six months and continued to be sustained up to 18 months. At 24 months, there was no statistically significant difference. Long-term safety was similar between the two groups.[48]

In a systematic review of 6 MCL601 studies, researchers found that incorporating MLC601 alongside conventional treatments may enhance both functional independence and motor recovery while also ensuring patient safety.[49] When MLC601 is accompanied by rehabilitation, it is possible that it could yield positive and enduring impacts on the neurorestorative process following a stroke.[50] A post-hoc analysis of the CMIMES study showed that patients receiving three months of MLC601 therapy had fewer side effects and lower rates of clinically impactful events, particularly in hospitalization duration.[51]

NeuroAiD does not induce significant alterations or adjustments in hematological, hemostatic, and biochemical parameters among both healthy individuals and stroke patients.[52] The MLC 901 was prescribed to a male patient with thalamic hemorrhage with intraventricular extension following shunt insertion. The patient was transferred to a rehabilitation center. At three- and six-month follow-up, there were significant improvements in deficits, and no adverse events were reported.[53]

In conclusion, although these neuroprotective agents hold great promise in stroke treatment, the results of the researches are still debating. Further clinical studies are required to assess the impacts of these agents on stroke patients. Randomized, placebo-controlled trials and head-to-head comparisons of these agents are needed to enhance our capabilities while treating such patients in neurorehabilitation clinics.

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