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Reperfusion Combined with Neuroprotective Agents Treatment in Acute Ischemic Stroke: a Literature Review of Current Progress

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Abstract: Acute ischemic stroke remains to be a heavy burden causing serious mortality and disability. Clinical studies of neuroprotective agents produced disappointing results in the treatment, and recanalization may be a precondition for it to be successful. By searching for relevant randomized controlled trials concerning combination therapy in the online databases and analyzing them, this literature review investigated the therapeutic effect of reperfusion combined with neuroprotective agents treatment in acute ischemic stroke. We found that reported trials specifically designed to investigate the efficacy of combination treatment are scarce. Overall, use of uric acid and nerinetide in the combination therapy exhibited positive results. These results indicate a high potential for clinical use with further confirmation. Future studies are still needed. They should focus on (1) designing clinical trials that investigate combination therapy specifically or include prespecified subgroup analyses for different types of recanalization, (2) reaffirming previous positive clinical trials with more patients of different characteristics or geographical locations, (3) employing multitarget neuroprotectant combinative therapy (cocktail therapy) to target multiple targets of ischemia-reperfusion injury instead of the currently prevalent single neuroprotectant with recanalization therapy.

Keywords: Stroke; Reperfusion; Neuroprotective; Combination Therapy

Introduction

A stroke is a severe emergency that the circulation to certain region of the brain is suspended. Stroke is an international health issue requiring worldwide attention. Stroke has two main types: ischemic and hemorrhagic. In the U.S., ischemic stroke accounts for 87% of strokes[1]. The damage caused by cerebral ischemia is not only the reduced supply of oxygen and glucose. Oxidative injury brought by the ischemia and recanalization treatment after is also critical. The two intertwine and contribute to the most part of the damage done by ischemic stroke[1].

As claimed by the American Stroke Association, clot removal is the predominant treatment for ischemic stroke, which can be accomplished by either medication or surgical means. Of all treatments, tissue plasminogen activator, r-tPA, (known as alteplase) is considered the gold standard. Some patients will receive mechanical thrombectomy especially when they have a large vessel occlusion[2].

Although restoration of blood flow to the occluded region as soon as possible remains to be the gold standard for acute ischemia stroke, considerable studies have shown that rapid recanalization could cause a cascade of complications[1]. The bleak outcome of current single therapy strategy and complexity of stroke pathophysiology call for additional treatment or combined treatment to help with the rehabilitation of acute ischemia stroke patients. This review intends to review the literature of reperfusion combined with neuroprotective agents treatment in acute ischemic stroke.

Main body

1. Existing treatment

1.1 Existing treatment: thrombolytics

Thrombolytics is the conventional treatment for stroke. Thrombolytics are clot-busting drugs that dissolve dangerous blood clots in the blood vessel. Thrombolytic agents can convert plasminogen into plasmin, which leads to blood clots lysis. Up till now, no less than three generations of thrombolytics with varying effectiveness, tolerability, and convenience are available[3].

Thrombolytics treatment is a tradeoff between the complication of hemorrhage and the possible recovery. The heterogeneity of the patients and lack of reliable approach to measure the treatment response make the quest for an ideal agent even harder. So far, despite the ever-improving therapeutic effect of new thrombolytics, the risk of hemorrhage is still an alarming side effect to be addressed[4].

1.2 Existing treatment: endovascular thrombectomy

Endovascular thrombectomy is a mechanical intervention that the blood clot is removed directly under image guidance. After the publication of five positive randomized controlled trials of thrombectomy in 2015, it became the new standard of treatment for stroke, especially for patients with large vessel occlusion[5,6].

Endovascular thrombectomy is performed most often by the use of stent-like thrombectomy devices. Retrievable stents are elastic stent-like devices that can be retrieved. The procedure has high recanalization rates with shorter time and fewer risk. However, there are some clinical situations that cannot be solved by stent retrievers. That's when the aspiration technique is employed. Overall, endovascular thrombectomy improve the recanalization rates, functional outcome, and reduce the disability of patients. The benefits apply to patients with different age and initial stroke severity and the overall therapeutic effect is better than the thrombolytics[1,2].

1.3 Existing treatment: neuroprotective treatment

Neuroprotection treatments have the potential to prevent or reverse the devastating cascade of acute ischemia stroke. It is generally accepted that their targets can be classified into four parts: excitotoxicity, reactive oxygen species, cellular apoptosis, and inflammation[3].

1.3.1Excitotoxicity

Acute ischemia stroke causes the decrease of energy and oxygen supply to the cell. The depletion of adenosine triphosphate (ATP) resulting from ischemia render the sodium/potassium (Na/K) transporter inoperable, thus increasing the intracellular calcium level. There is increased excitatory neurotransmitters level and activation of N-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Neuroprotective drugs targeting the calcium channel or NMDA and AMPA receptors may promote neuroprotection. Such drugs include clomethiazole, magnesium, repinotan, nerinetide, and so on[3].

1.3.2 Reactive oxygen species

Ischemia induced energy depletion renders the energy-dependent scavenger enzymes inactive. Then the reactive oxygen species build up in the affected area. Neuroprotective drugs that can degrade free radicals have the potential of neuroprotection. Such drugs include NXY-059, cerebrolysin, simvastatin, albumin, uric acid, and so on[3].

1.3.3 Cellular apoptosis

The ischemic conditions cause a cascade of signaling change. The downstream messengers ultimately induce cell apoptosis. Neuroprotective drugs that counter the apoptosis process have the potential of neuroprotection. Such drugs include imatinib and so on[3].

1.3.4 Inflammation

Cytokine released after the ischemia attract the resident microglia and immune cells from elsewhere which can destroy blood brain barrier and cause tissue damage. Neuroprotective drugs that have anti-inflammatory effect or immune suppressing effect have the potential of neuroprotection. Such drugs include erythropoietin, otaplimastat, and so on[3].

2. Combination therapy

This literature review reviewed the literature of reperfusion combined with neuroprotective agents treatment in stroke and investigate the therapeutic effect of combination therapy. This literature review primarily focused on random controlled trials research journals focusing on neuroprotection combined with reperfusion treatment in acute ischemic stroke. Studies were selected by searching electronic databases, i.e., Web of Science, PubMed, and so on. The search included studies up to March 10, 2023.

Reported trials specifically designed to investigate the combination treatment are scarce. Many of the reviewed literature were originally designed to test specific neuroprotective agents, yet some patients received thrombolytics, thrombectomy, or both as part of the standard

treatment during the process. Overall, use of uric acid and nerinetide in the combination therapy exhibited positive results. These results indicate a high potential for clinical use with further confirmation.

3. Discussion

Despite the bleak past of neuroprotection and the challenging road toward successful combination therapy, combination therapy is one of the most promising directions to improve the management of stroke. Future studies should focus on (1) designing clinical trials that investigate combination therapy specifically or include prespecified subgroup analyses for different types of recanalization, (2) reaffirming previous positive clinical trials with more patients of different characteristics or geographical locations, (3) employing multitarget neuroprotectant combinative therapy (cocktail therapy) to target multiple targets of ischemia-reperfusion injury instead of the currently prevalent single neuroprotectant with recanalization therapy.

This literature review is not without limitation. Despite rigorous literature collection process, not all studies investigating combination therapy for stroke can be acquired and analyzed. Plus, the available time for the research and writing is restricted. Further research encompassing larger sample size with more comprehensive analysis can be done to improve the review.

References

[1] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. Feb 21 2023;147(8):e93-e621. doi:10.1161/CIR.0000000000001123

[2] Martina Puzio NM, John J. O'Connor. Neuroprotective strategies for acute ischemic stroke: Targeting oxidative stress and prolyl hydroxylase domain inhibition in synaptic signalling. Brain Disorders. 2022;5

[3] McFarland J. Ischemic Stroke Treatment. American Heart Association. Available from: https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots/ischemic-stroke-treatment. [Accessed 8th March 2023]

[4] Lapchak PA, Araujo DM. Advances in ischemic stroke treatment: neuroprotective and combination therapies. Expert Opin Emerg Drugs. Mar 2007;12(1):97-112. doi:10.1517/14728214.12.1.97

[5] Bivard A, Lin L, Parsonsb MW. Review of stroke thrombolytics. J Stroke. May 2013;15(2):90-8. doi:10.5853/jos.2013.15.2.90

[6] Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. Apr 23 2016;387(10029):1723-31. doi:10.1016/S0140-6736(16)00163-X

[7] Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, Michel P. Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center. Stroke. Jul 2016;47(7):1844-9. doi:10.1161/STROKEAHA.115.012577

[8] Papanagiotou P, Ntaios G. Endovascular Thrombectomy in Acute Ischemic Stroke. Circ Cardiovasc Interv. Jan 2018;11(1):e005362. doi:10.1161/CIRCINTERVENTIONS.117.005362

[9] Link TW, Santillan A, Patsalides A. Intra-arterial neuroprotective therapy as an adjunct to endovascular intervention in acute ischemic stroke: A review of the literature and future directions. Interv Neuroradiol. Aug 2020;26(4):405-415. 1591019920925677. doi:10.1177/1591019920925677