Cerebroprotection and Mechanical Thrombectomy: A Powerful Combination?

Types of cerebroprotectants and their effects, why previous cerebroprotection trials have failed, current trials, and future directions.

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Endovascular treatment (EVT) (ie, mechanical removal of blood clots that obstruct blood flow in intracranial or cervical extracranial arteries) has dramatically improved outcomes of patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO). The number needed to treat for a 1-point improvement on the modified Rankin Scale is 2.6, one of the lowest throughout the entire field of medicine.[1] Nevertheless, despite major advancements in EVT and intravenous (IV) thrombolysis in recent years, up to half of all LVO stroke patients do not achieve functional independence, and there is still substantial room for improvement when it comes to AIS outcomes. Cerebroprotectants can be administered as adjunctive treatments in combination with EVT and IV thrombolysis and may be able to close this gap.

WHAT IS CEREBROPROTECTION?

Cerebroprotectants are treatments that protect brain tissue from ischemic damage. In the past, the term "neuroprotection" has been used; however, now, there is a tendency to refer to "cerebroprotection" instead, because the protective effect of these therapies is not only related to neuronal protection but also encompasses the protection of nonneuronal brain tissue components, such as glial and endothelial cells. A vast variety of cerebroprotective treatments have been proposed, all with different mechanisms of action that unfold their effect at different time points in the ischemic tissue damage cascade.[2]

Bridging cerebroprotectants aim to increase ischemia tolerance of the brain tissue and thereby prolong the time from onset of ischemia to irreversible tissue damage—they buy us additional time. Nerinetide, for example, is an agent with bridging cerebroprotective properties. As such, these types of cerebroprotectants could be particularly useful when transport times are long and EVT/thrombolysis treatment delays can be expected.

On the other hand, microvascular flow restorers act once recanalization of the occluded blood vessel has taken place. Examples of microvascular flow restorers include intra-arterial alteplase and tenecteplase. Macroscopic recanalization often does not lead to reperfusion of the downstream brain tissue because small arterioles and capillaries are obstructed by cellular debris, microthrombi, endothelial damage, and pericyte constriction. Microvascular flow restorers aim to reestablish the impaired reperfusion at the tissue level, such as by dissolving microthrombi.

Another example for postrecanalization cerebroprotection is the prevention of blood–brain barrier breakdown. Ischemia-induced damage to the endothelium and subsequent rapid inflow of blood into the previously ischemic area can lead to blood–brain barrier disruption and even frank parenchymal hemorrhage with mass effect. Blood–brain barrier stabilizers aim to support the integrity of the blood–brain barrier and thereby prevent extravasation of blood and inflammatory molecules from the intravascular to the extravascular compartment. Dl-3-n-butylphthalide, for instance, is a cerebroprotectant that has a stabilizing effect on the blood–brain barrier.

Finally, reperfusion injury preventers are another large group of cerebroprotectants that aim to prevent injury related to formation of reactive oxygen species, which happens when oxygen is reintroduced into previously ischemic tissue through recanalization and subsequent reperfusion. As an example, Veliparib (AbbVie) is thought to inhibit reperfusion injury–related tissue damage.

WHAT CEREBROPROTECTANTS CAN AND CANNOT DO

Cerebroprotection is not a causal treatment for AIS but rather a treatment effect enhancer for causal recanalizing treatments (ie, EVT and IV thrombolysis). Although bridging cerebroprotectants can increase ischemia tolerance of the tissue to some degree and thereby delay irreversible ischemic tissue damage, they cannot prevent such damage from happening. Reperfusion of the ischemic tissue is ultimately needed to save tissue. The misconception that cerebroprotectants can improve outcomes as a stand-alone treatment has been a source of confusion and frustration and may have been one of the main reasons why previous trials were not able to show clinical benefit of any cerebroprotectant in human AIS patients.[3]

WHY HAVE PREVIOUS CEREBROPROTECTION TRIALS FAILED?

Given that the concept of cerebroprotection sounds so appealing, why has no cerebroprotectant been approved for clinical use for AIS in humans? The answer lies in our understanding of the pathophysiology of tissue damage or, perhaps it is better to say, the lack thereof.

As mentioned previously, cerebroprotectants are not effective in saving brain tissue as a stand-alone treatment. They must be combined with a recanalizing therapy—EVT or IV thrombolysis—to have a beneficial effect. However, IV thrombolysis was the only approved recanalizing treatment until 2015, and it is only effective in a minority of LVO strokes. Thus, until very recently, reliable revascularization could not be achieved. This was a suboptimal setting for cerebroprotection trials and probably one of the main reasons why they failed. Now that EVT has become standard of care and has been broadly adopted in most industrialized nations, we have a human ischemia-reperfusion model at hand, and the conditions for testing cerebroprotective agents as adjunctive treatments are much better.

However, other problems are yet unsolved. For example, it is not clear which ischemic tissue damage mechanisms prevail in which patients. This knowledge is critical for choosing the right patients to enroll in a trial because different cerebroprotectants influence different tissue damage mechanisms to varying degrees. For example, due to preexisting microvascular impairment, blood–brain barrier breakdown may be more prevalent and/or cause more harm in diabetic stroke patients as compared with those without diabetes. Thus, researchers investigating the benefit of a blood–brain barrier stabilizer may want to include primarily diabetic patients in their early phase 2 trials because the treatment effect is expected to be largest in these patients. Similarly, there is limited knowledge on the exact time sequence in which different ischemic tissue damage mechanisms occur, leading to uncertainty regarding the optimal time point of cerebroprotectant administration. Ideally, these critical questions would be addressed first before designing additional cerebroprotection trials.

CURRENT TRIALS AND FUTURE DIRECTIONS

In 2020, the ESCAPE-NA1 trial showed that the cerebroprotectant nerinetide can improve outcomes in AIS patients with LVO undergoing EVT without concurrent IV alteplase.[4] In patients who received alteplase, no such benefit was seen, most likely due to a biological interaction between nerinetide and alteplase, whereby alteplase produces plasmin, which in turn cleaves and thereby inactivates nerinetide. ESCAPE-NA1 marked the end of a long series of unsuccessful human cerebroprotection studies, and there are more trials in the works. ESCAPE-NEXT (NCT04462536) aims to confirm the results of ESCAPE-NA1 in patients selected for endovascular revascularization without IV or intra-arterial thrombolytic therapy, and in the year 2022 there were 54 additional phase 1 to 3 human cerebroprotection trials registered on clinicaltrials.gov. However, obtaining more knowledge about the different tissue damage mechanisms will be paramount for the success of future cerebroprotection trials. We and others are conducting longitudinal imaging studies to gain a better in-depth understanding of these mechanisms. Finally, it seems that the time for cerebroprotection may be just around the corner. ■

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