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Multiphase adjuvant neuroprotection: A novel paradigm for improving acute ischemic stroke outcomes

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Abstract:

While several large pivotal clinical trials recently revealed a substantial benefit of endovascular thrombectomy for acute ischemic stroke (AIS) caused by large-vessel occlusion, many patients still experience mediocre prognosis. Enlargement of the ischemic core, failed revascularization, incomplete reperfusion, distal embolization, and secondary reperfusion injury substantially impact the salvaging of brain tissue and the functional outcomes of AIS. Here, we propose novel concept of "Multiphase Adjuvant Neuroprotection" as a new paradigm that may help guide our search for adjunctive treatments to be used together with thrombectomy. The premise of multiphase adjuvant neuroprotection is based on the diverse and potentially nonoverlapping pathophysiologic mechanisms that are triggered before, during, and after thrombectomy therapies. Before thrombectomy, strategies should focus on preventing the growth of the ischemic core; during thrombectomy, improving recanalization while reducing distal embolization and maximizing reperfusion are of significant importance; after reperfusion, strategies should focus on seeking targets to reduce secondary reperfusion injury. The concept of multiphase adjuvant neuroprotection, wherein different strategies are employed throughout the various phases of clinical care, might provide a paradigm to minimize the final infarct size and improve functional outcome in AIS patients treated with thrombectomy. With the success of thrombectomy in selected AIS patients, there is now an opportunity to revisit stroke neuroprotection. Notably, if the underlying mechanisms of these neuroprotective strategies are identified, their role in the distinct phases will provide further avenues to improve patient outcomes of AIS.

Keywords:

Acute ischemic stroke, endovascular thrombectomy, neuroprotection, penumbra, reperfusion injury

Introduction

Reperfusion, whether by thrombolysis, endovascular therapy, or a combination of these two methods, is the most effective therapeutic strategy for acute ischemic stroke (AIS).[1,2] For two decades, intravenous thrombolysis was the only effective reperfusion therapy for AIS.[3] More recently, several large pivotal clinical trials have demonstrated the superiority of endovascular thrombectomy (EVT) for patients with AIS caused by large-vessel occlusion when compared to medical management alone.[4-6] Despite its efficacy, only a small portion (approximately 10%) of AIS patients with large-vessel occlusion are eligible for thrombectomy, as most patients have a completed infarction on arrival to a thrombectomy-capable stroke center.[7,8]

Even with highly successful recanalization rates approaching 88%,[9-11] functional independence at 90 days is typically seen between 50% and 55% with mortality around 10%.[5,12] This counterintuitive mismatch between successful revascularization and mediocre prognosis calls for further investigation into underlying mechanisms

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and elucidation of strategies to improve functional outcomes of AIS patients undergoing thrombectomy. This review discusses the key challenges of improving functional outcomes among AIS patients treated with EVT, presents the concept of "Multiphase Adjuvant Neuroprotection" as a new paradigm to elucidate novel therapies for this patient population, and highlights several cautions regarding its implementation.

Key Issues Impacting the Final Infarct Volume

The primary goal of reperfusion therapy is to reduce the final infarct volume, a strong independent predictor of functional outcomes in patients with AIS caused by large-vessel occlusion.[13] The key issues that have a substantial impact on the final infarct volume, including further enlargement of the ischemic core, failed revascularization, incomplete reperfusion, distal embolization to new territories, and secondary reperfusion injury, are summarized.

Enlargement of the ischemic core

Arterial occlusion initiates the ischemic cascade[14] ultimately leading to cellular death and tissue necrosis. It is now widely recognized that not all territorial tissue is lost following arterial occlusion, but ischemic penumbra surrounding the ischemic core consists of salvageable brain tissue, which gradually evolves into irreversibly damaged tissue.[15] Collateral blood flow to the penumbral region is the key element setting the pace of the ischemic process and thus resulting in fast and slow infarction progressors.[16] Several studies have identified that good collaterals on initial presentation are associated with large volumes of salvageable brain tissue and good functional outcomes in AIS patients treated with thrombectomy.[17-19]

Due to these factors, reperfusion must be achieved as early as possible, especially in patients with poor collateral flow, to maximize penumbral salvage and minimize ischemic core. Unfortunately, even in developed countries, the time from symptom onset to eventual reperfusion frequently takes up to 4–5 h.[5,10,11,20] In addition, in the majority moderate- or low-income countries, large gaps remain between urban and rural emergency service systems, being particularly difficult for dispersed rural areas where there are limited health care resources, and long distance transport causes great delays in treatment.

Revascularization failure

Revascularization of the occluded vessel and restoration of cerebral blood flow is the most effective therapy to salvage penumbral brain tissue, and meaningful recanalization is the most powerful indicator of a good clinical outcome.[5,21] Recombinant tissue plasminogen activator (rtPA) is the mainstay drug for reperfusion therapy. It can initiate local fibrinolysis, leading to artery recanalization and improvement in functional outcomes if given within 4.5 h of presentation.[22-24] However, the current data indicates that only 30% of intracranial arterial occlusions can be recanalized by rtPA, and the ratio is much lower (approximately 10%) for large vessel occlusion.[25,26]

Recently, the superiority of EVT for AIS caused by proximal large vessel occlusion has been established, and a number of modern thrombectomy devices and techniques are currently available. Substantial recanalization following large-vessel occlusion can be achieved in up to 88% of patients immediately after thrombectomy procedures, significantly greater than traditional treatment.[4,6,10,11,27,28] However, there is still a large number of patients with a large-vessel occlusion that cannot achieve or maintain substantial recanalization, despite state-of-the-art approaches. Consequently, in these patients, salvageable brain tissue invariably progresses to irreversibly damaged tissue and infarction.

Incomplete reperfusion

Although revascularization of occluded large vessels is of vital importance to AIS patients, studies have found that angiographic recanalization of proximal large vessels, even in patients who achieved modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3, does not necessarily lead to complete distal reperfusion.[29-31] This phenomenon has been described as "no-reflow" or "incomplete microcirculatory reperfusion."[32] This incomplete reperfusion is seen secondary to underlying microcirculatory disorders caused by ischemic injuries, namely microvascular thrombosis, cerebral edema, and microemboli formation.[33-35]

Additionally, studies have found that patients with TICI 2b reperfusion have a poorer outcome than those with complete (TICI 3) reperfusion, indicating that reperfusion is a more accurate predictor of final infarct volume and functional outcome than simple proximal vessel recanalization.[29,36,37] Recent studies have proposed adding a new reperfusion grade of mTICI 2c (near complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli).[38] Studies have determined that mTICI 2c could further stratify subgroups of patients into mTICI 2b and mTICI2c/3 reperfusion, shifting the end goal of EVT.[39,40]

Distal embolization

During thrombectomy procedures with a stent retriever or direct clot aspiration, clot disruption and fragmentation is inevitable.[41] Clot debris may migrate

downstream with antegrade blood flow and can cause distal embolization in previously affected or unaffected vascular territories, potentially blocking collateral flow to salvageable tissue.[42,43] If thrombus fragments occlude large arterial branches, then remedial strategies such as further thrombectomy attempts or intra-arterial thrombolysis can be employed. However, *in vitro* studies show that the majority of clot fragments generated during thrombectomy are very small (<10 μm), occluding microvessels.[44,45] Although not detectable on angiogram, these distal microemboli translate to enlargement of ischemic core and poor functional outcomes.[42,43,46]

Reperfusion injury

Generally, revascularization promptly restores blood flow to the ischemic brain tissue and reduces enlargement of the ischemic core. However, restoration of blood flow also causes secondary injury through oxidative damage, cell death, and aberrant immunoinflammatory responses,[47-49] all of which can worsen the underlying ischemic injury. Consequently, reperfusion injury can result in brain edema, cell death, increased infarct volume, intracranial hemorrhage, headache, and seizure. Paradoxically, reperfusion in this way may aggravate neurological deficits and reduce its beneficial effects.[50,51]

Multiphase Adjuvant Neuroprotection

As mentioned previously, enlargement of the ischemic core, revascularization failure, incomplete reperfusion, distal embolization, and reperfusion injury substantially impact functional outcomes in AIS patients. Based on diverse and potentially nonoverlapping pathophysiologic mechanisms that are triggered before, during, and after thrombectomy, we propose the concept of "Multiphase Adjuvant Neuroprotection" to guide the search for adjunctive treatments aimed at minimizing deleterious ischemic injury. In the initial stages of ischemic stroke prior to thrombectomy, strategies should be used that enhance collaterals and block primary cell death mechanisms to prevent ischemic core enlargement. During thrombectomy, improving recanalization and maximizing reperfusion while reducing distal embolization is of primary importance. In the final phase, after reperfusion has been achieved, identifying targets within the cascades of secondary cell death mechanisms and inflammation can provide avenues to potentially ameliorate further reperfusion injury.

Based on previous studies investigating neuroprotection in AIS,[52-54] certain neuroprotective strategies can attenuate the growth of the ischemic core and ameliorate reperfusion injury, although variable maneuvers are needed in the various stages of stroke management. Previous studies have also shown that multimodal revascularization approaches can improve the rate of recanalization and reperfusion and prevent or limit distal emboli through the use of one or more devices and techniques.[55] The targets and approaches utilized during different phases of multiphase adjuvant neuroprotection are summarized and discussed in detail [Figure 1].

Before revascularization

Strategies for slowing the enlargement of the ischemic core should be used as early as possible, during the prehospital phase and throughout interhospital transfer, to maximize their ability to attenuate ischemic core growth. Ideally, they should meet the following requirements:

1. Fast-acting: The ischemic cascade starts immediately after arterial occlusion, and the ischemic core progresses quickly in patients with poor collaterals.[8] Therefore, ideal strategies should take effect as soon as possible to prevent enlargement of the ischemic core, especially for the fast progressors

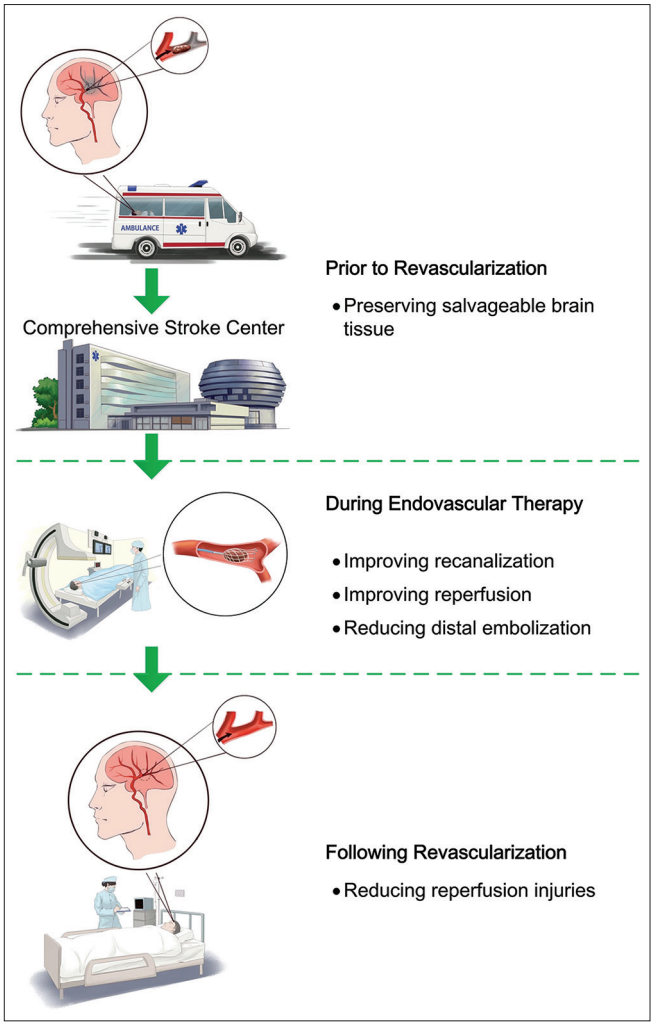

Figure 1: Multiphase adjuvant neuroprotection. Before revascularization, strategies should be used to prevent the enlargement of the ischemic core and preserve more salvageable brain tissue for reperfusion therapy. During endovascular therapy, strategies should be used to improve recanalization while reducing distal emboli and maximizing microcirculatory reperfusion. After reperfusion has been achieved, strategies should be used to reduce reperfusion injuries

2. Simple and usable: These strategies need to be initiated in prehospital settings and often by nonphysicians. As such, strategies that require special storage methods or complex preparation may limit their use
3. Safe and tolerable: Therapies employed in this phase must have a low risk profile, not only for AIS but also for hemorrhagic stroke and stroke mimics, given the difficulty distinguishing between these pathologies acutely
4. Do no harm: Most importantly, these strategies should not interfere with the effects of subsequent therapies, such as intravenous thrombolysis and thrombectomy.

Generally, neuroprotective drugs act directly on neurons, and thus, their neuroprotective efficacy depend on the presence of collaterals in the penumbra. Therefore, neuroprotective agents are typically ineffective with insufficient collaterals. This may partially explain why few neuroprotective drugs have translated into the clinical setting from preclinical models with limited efficacy in improving functional outcomes in clinical trials.[56] Fortunately, nonpharmacological approaches that meet the aforementioned requirements and have shown some success in preventing the enlargement of the ischemic core are available. Remote ischemic conditioning, a noninvasive and simple strategy, has been shown to be safe and feasible in AIS patients, reducing the risk of cerebral tissue infarction if applied during the prehospital phase.[57,58] One ongoing trial investigating remote ischemic conditioning performed ahead of hospital in acute stroke patient is ongoing (clinicaltrials.gov NCT 03481777). In addition, another ongoing trial specially investigated remote ischemic conditioning in AIS patients treated with EVT (clinicaltrials.gov NCT03045055). Additionally, normobaric oxygen can slow the progression of cell death, extend the time window for revascularization therapy, and salvage ischemic brain tissue.[59,60] Preliminary safety, feasibility, and efficacy of this strategy have been demonstrated in a recent clinical trial.[61]

In clinical practice, many patients first arrive at primary hospitals that are not capable of thrombectomy or intravenous thrombolysis and are subsequently transferred to a comprehensive stroke center for reperfusion therapies. For these patients, the ischemic stroke and absence of intracranial hemorrhage is usually diagnosed by computed tomography in the initial hospital. Therefore, neuroprotective strategies, unsuitable for hemorrhagic stroke, can also be used. Induced hypertension with appropriate range (systolic pressure of 160 mmHg) can be used to assist in the maintenance of cerebral collaterals, which are of vital importance in supporting brain tissue in the penumbra.[62] Furthermore, neuroprotective strategies not available in the prehospital phase due to special storage methods or complex preparation requirements may also be available in the primary hospital setting.

During endovascular therapy

Improving recanalization

Currently, stent retriever thrombectomy and direct clot aspiration are the two seminal thrombectomy techniques, and many modifications to these techniques have emerged. Novel approaches, devices, techniques, and strategies have been discussed in detail in other reviews.[9,63-66] It should be note that achieving complete recanalization with the simplest techniques and the least manipulation should be the primary goal of EVT.[67,68]

Improving reperfusion and reducing distal embolization

As previously stated, ischemic injury, microvascular thrombosis, cerebral edema, and microemboli are the main causes of incomplete reperfusion. Ischemic injury causes cytotoxic edema, resulting in microcirculatory disturbances and microvascular thrombosis.[33] Neuroprotective agents or other neuroprotective approaches that attenuate ischemic injury may be effective in preventing microcirculatory disturbances, enhancing complete reperfusion.[69] Furthermore, distal emboli, most of which result from downstream migration of clot debris, also contribute to incomplete reperfusion,[33] and efforts have been made to improve thrombectomy techniques to reduce this phenomenon. In addition, to identify microvascular hypoperfusion and its extent, perfusion imaging is also needed after successful revascularization on angiogram images.

Balloon guide catheters can be used to block antegrade blood flow during thrombus retrieval, significantly reducing distal emboli.[70] Many thrombectomy techniques, with or without balloon guide catheters, use large-bore aspiration catheters that employ negative pressure to continually aspirate blood during thrombus retrieval, also reducing distal embolization.[71,72] However, even using these techniques, distal emboli in the affected and previously unaffected vascular territory is still common.[10,28,35] Therefore, technological innovations and development of novel devices and techniques to limit clot fragmentation and distal emboli are still needed.[73]

If distal embolization does occur, appropriate therapeutic strategies are needed for remediation. As the majority of distal emboli are very small and cannot be detected by angiography, distal drug infusion may be an appropriate treatment. Studies have determined that tirofiban, a glycoprotein IIb/IIIa antagonist, is effective in preventing microvascular thrombosis and improving functional outcome in AIS, with no increase

in intracerebral hemorrhage if administered at a low dose.[9,74] Intravenous or intra-arterial administration of thrombolytic agents (such as rtPA and urokinase) has been reported as an effective remedial strategy for the treatment of distal emboli as well,[66,75] but safety and efficacy considerations necessitate further investigation.

Following revascularization

In the past few decades, reperfusion injury has been extensively investigated with numerous neuroprotective strategies having been proposed. Despite promising results in preclinical models, few of them have translated to clinical benefit in human trials.[56] Inappropriate selection and inclusion of patients with poor rates of meaningful recanalization may underlie the lack of clinical efficacy. Furthermore, most neuroprotective strategies generally target a single pathway in the complex ischemic cascade.[76] With the substantial increase in AIS patients being treated with mechanical thrombectomy and higher rates of recanalization, several nonpharmacological approaches targeting multiple pathways of the ischemic cascade are now available.[77] With the increased number of patients achieving recanalization, it is plausible that combining reperfusion therapies with adjunctive pharmacological and nonpharmacological approaches could have synergistic effects.

Numerous neuroprotective pharmacological approaches have been investigated, although few have shown clinical beneficial. NXY-059, a free radical-trapping agent, reduces infarct size and preserves neurologic function in animal models of AIS.[78] Despite preclinical efficacy, results of large clinical trials showed that NXY-059 administered within 6 h after symptoms onset did not improve functional outcomes in AIS.[79,80] Another agent, magnesium, exerts both neuroprotective, vasodilatory, and glioprotective effects. Magnesium is reliably neuroprotective in animal models of AIS, a good safety profile, widely available, inexpensive, and simple to administer.[81] Unfortunately, a clinical trial with 1,700 subjects found that, while prehospital initiation of intravenous magnesium was safe and feasible, it did not improve clinical outcomes.[82] Importantly, these clinical trials recruited patients who had not undergone endovascular therapies, achieving low rates of recanalization. The effect of NXY-059 and magnesium in patients with definitive revascularization remains uninvestigated.

Although neuroprotective drugs for clinical application are currently lacking, novel pharmacological approaches are emerging. For example, NA-1, a cell-permeant eicosapeptide, is a promising agent that inhibits the interactions of the synaptic scaffolding protein PSD95 with NMDA glutamate receptors.[83] NA-1 has been found to reduce infarct size in both rat and primate model of AIS.[84] Furthermore, clinical evaluation of NA-1 in patients undergoing endovascular aneurysm embolization found that it could reduce the incidence and size of iatrogenic infarct following treatment.[85] Positive results have been seen in preclinical stroke models, including rodent and nonhuman primates, and two large clinical trials investigating NA-1 in AIS are ongoing. One trial, FRONTIER (Field Randomization of NA-1 Therapy in Early Responders trial, NCT02315443), is investigating the safety and efficacy of prehospital intravenous NA-1 in the field for AIS within 3 h of symptom onset. Another trial, ESCAPE-NA-1 (The Extension of Stroke Care by Adding neuroProtection to Endovascular treatment trial, NCT02930018), is evaluating the efficacy of NA-1 in AIS patients undergoing EVT.

In contrast to other patient populations, AIS patients treated with thrombectomy can receive neuroprotective agents delivered, not only through peripheral venous access, but also through arterial catheters that provide direct access to the ischemic tissue. This could easily be performed during EVT, increasing the drug concentration administered to the local cerebral tissue. Finally, intra-arterial selective cooling, a promising nonpharmacological treatment, can easily be performed shortly after thrombectomy to induce partial hypothermia in the ischemic area.[86-89] In previous pilot study, intra-arterial selective cooling has been performed in AIS undergoing EVT.[90] Cold 0.9% sodium chloride (4°C) was infused to the ischemic territory before recanalization (10 ml/min for 5 min) through microcatheter and postrevascularization (30 ml/min for 10 min) through the guiding catheter. Currently, a phase II study is ongoing to investigate the efficacy of short-duration selective brain cooling in AIS treated with EVT (clinicaltrials.gov NCT 03163459).

Distinct Neuroprotective Approaches in Different Phases of Care

Prior to initiating neuroprotective strategies for AIS, caution should be taken as many molecular pathways in the ischemic cascade have biphasic natures. For example, overactivation of N-methyl-D-aspartate receptors is clearly detrimental in the early phase of stroke, but these same receptors may be required for recovery later in the process.[91] Another example is matrix metalloproteinase, which damages the blood–brain barrier and causes edema, hemorrhage, and neuronal death in the early stage of stroke,[92] but promotes neurovascular remodeling in the delayed stage.[93] Unfortunately, it is not entirely clear when these molecular signals transition from injury to repair and what initiates or triggers these transitions. Considering

the biphasic roles, neuroprotective strategies that target different molecular signals should be applied only in distinct phases of stroke management. Further elucidation of these pathways and biomolecular responses is of great significance for clinical trials, as they can guide the administration of neuroprotective strategies accurately and effectively. Given these concerns, it is advisable to use neuroprotective strategies that have proven efficacy in a certain phase of the stroke, to reduce the possibility of targeting molecular signals in a haphazard or counterproductive manner.

Conclusion

In an era where reperfusion is seen with increasing frequency, enlargement of the ischemic core, revascularization failure, incomplete reperfusion, distal embolization, and reperfusion injury represent potential factors that negatively impact outcome following AIS. Utilizing a concept of multiphase adjuvant neuroprotection, wherein different strategies are employed throughout the various phases of clinical care, provides a paradigm to minimize the final infarct size and improve functional outcome in AIS patients treated with thrombectomy by tailoring neuroprotective measures to all phases of stroke management. Many neuroprotective approaches still need to be tested, alongside development of new generations of reperfusion strategies. As the underlying mechanisms of these neuroprotective strategies are identified, their role in the distinct phases of ischemic stroke care may provide further avenues to improve patient outcomes in this debilitating disease.

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Conflicts of interest

There are no conflicts of interest.

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