Title
Reconsidering Neuroprotection in the Reperfusion Era.

Permalink
https://escholarship.org/uc/item/5tr4q95c

Journal
Stroke, 48(12)

ISSN
0039-2499

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Publication Date
2017-12-01

DOI
10.1161/strokeaha.117.017283

Peer reviewed
Neuroprotection to prevent infarct progression as a potential treatment for acute ischemic stroke carries a long and disappointing history. The failures of these prior neuroprotection trials have many potential explanations that encompass both problems with the preclinical assessment of these drugs and the design/implementation of clinical trials. Prior development of neuroprotection has focused primarily on its use as a monotherapy, and no clinical trial was designed to determine whether neuroprotection could extend the time window for successful reperfusion and ameliorate the consequences of reperfusion. Acute stroke therapy has now entered the era of highly effective reperfusion with the recent publication of 5 positive thrombectomy trials. Combining neuroprotection with intravenous or intra-arterial reperfusion therapy is now an important next step in the development of acute stroke therapies. One approach to neuroprotection would be to initiate therapy early after ischemic stroke onset, either in the ambulance or at a primary stroke center/community hospital to potentially extend the time window for intravenous or intra-arterial therapy. A second approach would be to use neuroprotection during or after partial or complete reperfusion to reduce the consequences of reperfusion injury. Both future neuroprotective approaches will require preclinical studies that anticipate novel clinical trial designs and trials that will be organized and evaluated differently than past monotherapy neuroprotection trials.

Ischemic Penumbra and Core

Acute ischemic stroke therapy is designed to reduce infarction of hypoperfused brain tissue and limit the expansion of already irreversibly injured tissue when treatment is initiated, leading to smaller infarction and improved clinical outcomes. Severely hypoperfused but still potentially viable ischemic brain represents the ischemic penumbra, whereas irreversibly injured tissue is the ischemic core. Early after stroke onset, most patients with a large vessel occlusion (LVO) have an extensive ischemic penumbra that can be salvaged by timely reperfusion. This concept was proven directly and indirectly in the thrombectomy trials where patients with proximal LVOs were included only if they had small to moderate sized ischemic cores as identified by computed tomographic (CT) perfusion or the ASPECTS score (Alberta Stroke Program Early CT Score) on plain head CT and a substantial amount of ischemic tissue at risk of infarction. Rapidly performed thrombectomy with devices that recanalize most to all of the vessel occlusion in such patients led to the remarkably positive 90-day clinical outcomes observed in the thrombectomy trials. Patients with large ischemic cores are not likely to have the same benefit from thrombectomy; thus, when there is a substantial delay in performing thrombectomy because patients need to be transported long distances to an endovascular capable center or the thrombectomy team is not immediately available, the ischemic core may enlarge to a degree that the procedure cannot ensure good outcome. Similarly, for intravenous thrombolysis, the beneficial effect of tissue-type plasminogen activator diminishes substantially over time, likely also reflecting growth of the ischemic core. The question is, therefore, whether core volume can be kept as small as possible until reperfusion takes place?

Can neuroprotection be utilized to slow down the growth of the ischemic core, preserve at risk penumbral tissue, and increase the number of patients successfully treated with intravenous thrombolysis or by thrombectomy? Animal studies do suggest that neuroprotective drugs or high flow oxygen can impede the evolution of penumbra into core. An extension of the therapeutic time window for tissue-type plasminogen activator has been observed in animal stroke models, but such experiments in animal thrombectomy models have yet to be performed. Based on the animal studies of the effects of neuroprotection on penumbral evolution and extension of the time window for intravenous thrombolysis, it can be anticipated that neuroprotection given early after ischemic stroke onset may extend the time window for beneficial thrombectomy. As discussed in this review, clinical trials are anticipated in which a neuroprotective drug is initiated in the ambulance or at an outlying hospital in patients who are likely thrombectomy candidates based on their LVO pattern. The primary end...
point of such trials would be the percentage of patients who are thrombectomy candidates by accepted criteria on reaching the comprehensive stroke center or a direct comparison of ischemic core volume or infarct growth in the treated versus control group as measured by CT perfusion or diffusion-weighted magnetic resonance imaging. Several approaches, pharmacological and nonpharmacological, to freeze the penumbra and minimize expansion of core volume are currently being tested in the laboratory and clinical trials.

Pharmacological Approaches

Focal cerebral ischemia unleashes a complex of array of biochemical processes termed as the ischemic cascade that leads to cell death of neurons and various other brain cells. Neuroprotective agents have been designed to affect different pathways in the ischemic cascade. These drugs can be categorized based on their mechanism of action. The main categories include agents that inhibit glutamate mediated signaling, calcium signaling, free radicals, or inflammation. Some drugs have been found to exert multiple modes of action on these pathways. During the past 30 years, dozens of drugs that have been found to be neuroprotective in animal stroke models have been brought forward to clinical trials. Unfortunately, none of these drugs have been found to reproducibly improve outcome in pivotal phase III efficacy trials.

Some of the lessons learned from these failures have recently been implemented. Drugs are tested in animal models with more rigorous methodologies to improve the internal validity of the results. Clinical trials are now better designed to detect possible effects of neuroprotective agents by studying early time windows after stroke onset. With the approval of new recanalization therapies with mechanical thrombectomy, 4 main ways that we envision neuroprotective agents should be tested in animal models of stroke are the following:

- Extending the window of thrombolytic therapy: although neuroprotective agents have largely been studied as monotherapies in animal stroke models, far less research has been devoted to studying neuroprotective agents in the context of thrombolysis. A few neuroprotective agents have been tested in combination with intravenous tissue-type plasminogen activator (tPA). For example, minocycline intravenous administered at 4 hours after the onset of ischemic stroke has been shown to extend the therapeutic time window of intravenous tPA to 6 hours. Thromboembolic models are challenging to conduct and require highly specialized laboratories skilled at controlling the variables of clot preparation, insertion, and treatment with tPA. However, the embolic model is likely the most relevant to test neuroprotective agents in conjunction with tPA.

- Prevent or retard infarct expansion in patients with large artery occlusion requiring endovascular treatment: we would envision that neuroprotective agents be tested in large animal stroke models that permit testing in the context of thrombectomy. Animal models of dogs and nonhuman primate models have successfully been developed for embolic cerebral arterial occlusion and thrombectomy. These models could be used to test the hypothesis that neuroprotective agents extend the time window for thrombectomy in large artery occlusions.

- Additive effect of neuroprotection with intra-arterial therapy: established rodent models of focal ischemic stroke by conventional means, such as middle cerebral artery (MCA) suture occlusion, still retain value as an approach to test the additive effects of neuroprotective agents in the setting of reperfusion. This model does simulate some of the clinical aspects of thrombectomy in LVO and would be useful when considering trial designs of neuroprotective agent initiated before thrombectomy.

- Intra-arterial delivery of neuroprotective agents: immediately after endovascular thrombectomy, neuroprotective agents could be delivered selectively into the previously hypoperfused brain with an intra-arterial injection. New animal studies are starting to emerge that agents, previously found to be neuroprotective by intravenous administration, exert profound beneficial effects on tissue salvage. Selective intra-arterial delivery is undergoing initial clinical study.

Repurposing Prior Drugs

Given the various applications of neuroprotective agents in the context of reperfusion or planned reperfusion, there are a multitude of drugs that have been previously tested and found to be neuroprotective in animals. Which drugs previously brought forward to clinical trials should be repurposed? We envision convening a panel of scientists and clinician-researchers to rank order the most highly promising compounds previously tested or to consider new agents that show robust efficacy in preclinical models. It would be important to define criteria for drugs that were tested rigorously in animal models and if sufficient and clinically relevant testing has been conducted to advance promising agents forward in new clinical trials. Several initiatives, conferences, and publications have called for the creation of preclinical stroke networks consisting of laboratories that would test neuroprotective compounds to address reproducibility of results and provide a wide array of models to assess robustness of effects.

Nonpharmacological Neuroprotective Approaches to Freeze the Penumbra

Nonpharmacological approaches to freeze the penumbra are particularly attractive because they are generally noninvasive and easy to administer, and thus could be initiated in the ambulance or even prehospital, in-the-field. According to the concept of freezing the penumbra, such ultra-early interventions would enhance the therapeutic effects over and above reperfusion therapy. To be applicable, nonpharmacological approaches would need to be safe in stroke mimics and intracerebral hemorrhage. Although Phase II proof-of-concept randomized control trials (RCTs) have already established the feasibility and safety of some of these approaches, as of today none have been shown to be efficacious. Based on the well-validated penumbra model derived from positron emission tomography, 2 main approaches to freeze the penumbra can be considered: (1) enhancing oxygen delivery to the penumbra by increasing oxygen transport or collateral flow, or both; and (2) reducing the brain tissue’s oxygen demand.

Normobaric hyperoxia (NBO) is a well-studied nonpharmacological approach to freeze the penumbra. Extensive work in
rodents has established that NBO increases penumbral Po$_2$ ≥2-fold. Twenty published studies have assessed the effects of NBO after MCA occlusion (MCAo) in rodents. Across studies, NBO reduced infarct volume if administered early after transient MCAo. With long durations beyond 180 minutes or permanent MCAo (pMCAo), the benefit was usually nil or marginal. The effective arrest of apparent diffusion coefficient lesion growth observed during NBO in rodents illustrates and validates the concept of freezing the penumbra. An important feature for clinical translation is the decline of NBO’s beneficial effects as time elapses after MCAo. With pMCAo, the earlier NBO is initiated, the greater the benefits. Equally important for clinical translation, NBO does not interfere with tPA in rodent models, has no obvious side effects in combination with tPA, and can be continued with tPA. No detrimental effects occur with experimental intraparenchymal hemorrhage.

Both published Phase II RCTs of NBO documented feasibility and safety but found no clinical benefit. However, neither tested the penumbral freezing concept, that is, NBO was not combined with recanalization and study candidates for reperfusion were excluded. However, in 1 trial, lesion growth stopped and clinical deficits improved during the 4-hour NBO regimen, but lesion growth subsequently resumed after NBO was stopped, as predicted by the penumbral model. A subsequent larger trial was terminated prematurely because of increased mortality in the active arm, although the increased mortality was not directly attributed to NBO (https://clinicaltrials.gov/ct2/show/NCT00414726). An RCT recently funded by the European Union (acronym: PROOF [Penumbral Rescue by Normobaric O$_2$O Administration in Patients With Ischemic Stroke and Target Mismatch Profile]) is designed to directly test the penumbral freezing hypothesis by including only candidates for reperfusion therapies. An extension to the NBO approach would combine it with perfluorocarbon infusion to further increase oxygen blood content and tissue delivery.

Another approach to increase oxygen delivery to the penumbra is to enhance collateral flow to circumvent the proximal occlusion until reperfusion is achieved. Several general physiological measures, such as head-down bed position, hypervolemia, and pharmacologically induced hypothermia, are sometimes practiced as part of standard clinical care in the absence of evidence from RCTs. Another approach is transient descending aortic balloon occlusion to increase perfusion in the brain and has been tested in rodents with positive results. The SENTIS phase 2b trial (Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke) showed safety of this approach but no hint of efficacy; however, again candidates for reperfusion therapies were excluded. Perconditioning using upper forepaw stimulation delivered early after MCAo. A pilot safety RCT is in the planning stage.

Reducing the demand of ischemic tissue for oxygen is another potential method to freeze the penumbra. Particularly attractive is moderate whole-body hypothermia, which induces strong neural inhibition and consistently reduces infarct volume in animal models. Unfortunately, effective hypothermia is relatively cumbersome to implement in the clinical setting and hard to envision before reperfusion. No trial currently aims specifically at freezing the penumbra using hypothermia. Cathodal transcranial direct current stimulation also aims at neuronal inhibition and was reported in 2 temporary MCAo rodent studies to modestly reduce infarct volume, apparently by blocking peri-infarct depolarizations. A safety and feasibility Phase II RCT has recently started in France.

Reperfusion Injury: A Pharmacological Target After Successful Reperfusion?

Although a major goal of acute stroke treatment is the restoration of cerebral blood flow, this approach can lead to worsened damage, a phenomenon known as reperfusion injury. Although less clear in clinical stroke, reperfusion injury has been well documented in experimental stroke models. Evidence at the experimental level for reperfusion injury includes numerous observations of laboratories that use transient MCAo models in comparison with pMCAo. Several investigators have noted that when MCAo occurs for prolonged durations followed by reperfusion, the resulting infarct size is actually larger than that seen under conditions of pMCAo. Although the precise duration of MCAo that leads to reperfusion injury varies from laboratory to laboratory, it seems that the longer the MCA is occluded, the greater the likelihood of causing increased lesion size. One comparative study showed that MCAo in rodents of durations of 2 hours or longer followed by reperfusion led to larger infarct sizes compared with pMCAo in some rat strains.

Clinical evidence for reperfusion injury is less clear. Many clinicians observe a reperfusion syndrome characterized by headache, transient brain edema, and hemorrhagic transformation after surgical or pharmacological revascularization, and this phenomenon is often accompanied by hyperperfusion. However, the syndrome is thought to be rare and it is unclear whether it leads to permanent worsened outcome. A clinical imaging study also indicated that reperfusion increased the likelihood of blood brain barrier disruption on magnetic resonance imaging in patients treated with tPA. The short time window for thrombolytic treatment is also a result of an increased risk of significant brain hemorrhage and worsened outcome if thrombolytics are administered a few hours poststroke. The worsened outcome from pharmacological thrombolysis is usually because of significant brain hemorrhage into the area of infarction, which is also a consequence of reperfusion. Thus, identifying treatment strategies to target reperfusion injury has the potential to reduce the risk of poor outcomes after thrombolysis or mechanical thrombectomy and possibly extend the time window for intervention.

The mechanism of reperfusion injury has largely been viewed as the sudden introduction of oxygenated blood into ischemic tissue. Oxygenated blood allows the entry of
reactive oxygen species (ROS), which overwhelms the endogenous antioxidant capacity of ischemic brain cells. ROS can also directly damage mitochondria, proteins, DNA, and lipids. ROS can also act as signaling molecules, which can activate cell death pathways, such as apoptosis. ROS and ischemia itself can damage cerebral blood vessels within the area of the stroke causing them to be leaky and permit entry of serum proteins and blood, all of which can lead to brain edema and hemorrhage. Substantial laboratory work has shown evidence for ROS-mediated injury in stroke models, and a variety of antioxidants improve outcome from experimental stroke and also reduce brain edema, brain ROS, and hemorrhage. Further, genetic models of rodents lacking or overexpressing endogenous antioxidants have consistently shown worsening or improvement of stroke outcome, respectively.

Another component of reperfusion includes the contribution of the immune system. Stroke leads to activation of the brain’s endogenous immune cells, the microglia, as well as activation of circulating immune cells and ischemic endothelium. Circulating leukocytes home to areas of activated endothelia and bind to adhesion molecules that allow infiltration into ischemic tissue. Once leukocytes and activated microglia enter ischemic brain tissue, they elaborate various proinflammatory molecules, such as cytokines, chemokines, complement, inducible NO synthase, and, of course, more ROS. Immune cells are also capable of expressing proteases, such as the matrix metalloproteinases, which can further disrupt the extracellular matrix and lead to brain hemorrhage. Preventing the infiltration of circulating leukocytes or microglial activation has been shown in the laboratory to improve outcome from experimental stroke, as well as inhibiting several immune targets. Unfortunately, although this strategy was shown to be effective in the laboratory, clinical trials of similar approaches have shown to be either not effective or led to worsened outcome, although 1 small open-label trial of minocycline to inhibit microglial activation seemed to have a positive effect on patients with stroke.

Hyperglycemia also contributes to reperfusion injury and is known to worsen outcome from stroke at both the clinical and experimental levels, and significant hyperglycemia also increases the risk of brain hemorrhage in the setting of rt-PA use. Hyperglycemia can contribute to reperfusion injury through a proinflammatory mechanism. NADPH oxidase is a major source of superoxide generation originally described in immune cells. Glucose is required for the enzymatic functions of NADPH oxidase because its metabolism through the hexose monophosphate shunt leads to electron transfer of O2 to NADP+, thus generating superoxide (O2−). Laboratory studies have shown that glucose must be present in the reperfusate to generate superoxide in cell culture studies, and inhibition of NADPH oxidase can prevent worsened reperfusion injury because of hyperglycemia. Thus, controlling serum glucose levels may be important in limiting reperfusion injury. Another promising treatment that may target oxidative injury in ischemic stroke exacerbated by hyperglycemia is uric acid. Post hoc studies of the URICOICTUS trial have shown possible benefits of uric acid in those patients with early reperfusion, good collaterals, or pretreatment hyperglycemia.

Because there are now proven effective treatments for reperfusion, the possibility of pursuing dedicated clinical studies of adjunctive treatments targeting oxidative stress and inflammation along with pharmacological thrombolysis and mechanical thrombectomy exists. Especially in the context of reperfusion injury, the vessel interface has also become an important target for protective therapies, a strategy referred to as vasculoprotection. Such approaches would include regulating endothelial cell integrity and treating blood brain barrier disruption.

Neuroprotectant Trial Design and Implementation

Setting of Neuroprotective Therapies in Stroke

One of the fundamental decisions in neuroprotective trial design is to select the most appropriate setting in which to initiate therapy (Figure). Initiation within the first hour after symptom onset would necessitate a prehospital approach. Trials of prehospital therapy require a completely different type of research study apparatus, which may increase cost and reduce the number of possible neuroprotective agents eligible for testing. Most common clinical trials of neuroprotection for stroke have opted for initiation after hospital arrival, after imaging and initiation of thrombolysis. However, other options that are intriguing but not well studied are post emergency department (ED) arrival before imaging, during secondary transport, just before endovascular thrombectomy, and immediately post-thrombectomy using the same catheter for an intra-arterial delivery.

Prehospital

Many patients with stroke arrive to the ED by ambulance, and emergency medical service providers are trained in the use of validated prehospital stroke recognition tools. Systems of stroke care supporting prehospital initiation include triage/routing of potential patients with stroke to designated stroke centers.
center hospitals. Although prehospital therapy allows for rapid initiation of potential neuroprotectants, it has important limitations, including need to select agents known to be safe in intracerebral hemorrhage, higher rates of stroke mimics, need for storage in ambulances, and easy initiation by paramedics. If an agent cannot be stored at temperatures commonly encountered in the ambulance, it could only be tested in the prehospital setting if refrigeration is available. A therapy requiring compounding by paramedics could be challenging and requires extensive training, limiting its applicability. The clinical trial apparatus for prehospital research has to involve regions with well-developed emergency medical service networks rather than individual hospitals. Issues of informed consent are central to clinical trial design in the prehospital setting.

There have been clinical trials of prehospital neuroprotective therapy for stroke, including 1 phase III study of intravenous magnesium (Table) and 2 active clinical trials that are enrolling (Table). Although a neutral study, the National Institutes of Health–funded FAST-MAG clinical trial (Field Administration of Stroke Therapy Magnesium) demonstrated that neuroprotective therapy can be started 45 minutes after stroke symptom onset.40 Subjects in FAST-MAG were exposed to study agent for 92 minutes before receiving tPA and 230 minutes before the start of endovascular therapy (unpublished data). With the advent of mobile stroke units that have CT scanners in the ambulance, we can envision that prehospital neuroprotection studies will be conducted in the future by stroke neurologists either physically present in the ambulance or by telemedicine.41 Agents that have not been tested for safety in preclinical models of hemorrhage or that have any potential effect on coagulation would not be testable in the prehospital setting, not until after neuroimaging is obtained, necessitating a start in the hospital, after imaging and decisions on thrombolysis have been made. It is unlikely that an agent with these limitations could be tested less than an hour after symptom onset unless the study was conducted in a mobile stroke unit.

Table. Important Conditions to Consider for the Application of Neuroprotective Agents

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<tr>
<th>Desirable for prehospital use</th>
<th>Desirable for preintervention use</th>
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<tbody>
<tr>
<td>Safe in intracerebral hemorrhage</td>
<td>Targets reperfusion injury or other mechanisms relevant in the time period</td>
</tr>
<tr>
<td>Ease of administration and preparation in the field</td>
<td>No need to worry about ease of storage (can be stored/mixed in central pharmacy)</td>
</tr>
<tr>
<td>No interaction with tPA</td>
<td>Can have complicated dosing</td>
</tr>
<tr>
<td>Clinical/experimental data demonstrating increasing efficacy with earlier administration</td>
<td>Select ideal cases so less numbers enrolled</td>
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tPA indicates tissue-type plasminogen activator.

Posthospital Arrival Preimaging

On arrival to the ED, patients with stroke are taken directly to neuroimaging. The rapid evaluation for thrombolytic candidacy limits the ability to obtain informed consent. Although untested, 1 possible approach is use of exception from informed consent to initiate therapy immediately on ED arrival, before imaging. Advantages are earlier treatment initiation, the ability to screen enrollees using hospital-based stroke tools like the National Institutes of Health Stroke Scale, and study neuroprotective agent storage in a controlled environment (refrigerator), all of which would have to be weighed against drawbacks such as testing only agents with safety in intracerebral hemorrhage and obtaining community and institutional review board approval of exception from informed consent.

Postarrival Postimaging (Including Secondary Transport)

The most common scenario in which neuroprotectants have been tested in stroke is postimaging and after intravenous thrombolysis has been decided. This approach allows time for obtaining informed consent and for exclusion of patients with intracerebral hemorrhage. Clinical trials enrolling in this time period have typically had time windows of <6 hours from onset leading to initiation times averaging 3 ¾ hours into hospital course.42 Some studies in this setting include combination of neuroprotective approaches with intravenous thrombolysis.43,44

The emergence of endovascular thrombectomy as the standard of care for LVO has led to the development of rapid transfer systems of care to obtain eligible patients to comprehensive stroke centers. There are 3 possible methods to triage LVO to endovascular centers:

- Secondary transport (drip and ship): prehospital transport to the closest stroke center for earlier intravenous thrombolysis and in-hospital screening for LVO followed by secondary ambulance/helicopter transport to an endovascular center.
- Primary transport (straight to the mothership): prehospital transport directly to the endovascular center in cases where prehospital LVO screen is positive, bypassing closer stroke centers, leading to potentially slower intravenous thrombolysis but faster endovascular thrombectomy.
- Mobile stroke units: intravenous tPA administered in the mobile stroke units, if CT angiography or clinical scale indicates LVO, then transport to endovascular center during tPA infusion.

Transport times vary greatly by region, and in some cases may involve great distances and times. Neuroprotection during transport in all of these 3 scenarios could be an effective strategy and needs to be tested.

Pre-Endovascular Thrombectomy

Patients with LVO undergoing thrombectomy have a high likelihood of successful reperfusion. Neuroprotective agents could be stored in the ED or hospital pharmacy and administered before thrombectomy. Agents could target reperfusion injury and there would be sufficient time to obtain informed consent.
Novel Clinical Trial Design

New drug development is a time-consuming and expensive process. The Federal Drug Administration released critical path initiatives encouraging innovative adaptive clinical trial designs. Adaptive clinical trials have prespecified modifications in their design in response to data generated, allowing for greater flexibility. Adaptive design is intended to cut costs and reduce time to successful translation of therapies. Adaptive clinical trial designs have not been sufficiently used for neuroprotective agents in stroke. Classically, many single agents have been advanced from the laboratory through phases of clinical testing, ultimately failing along the way. Adaptive clinical trial design is attractive for phase II testing with the potential for testing multiple agents concurrently when there is absence of a single consensus agent to advance to phase III. To this end, Bayesian MAMS studies (Multi-Arm Multi-Stage) of multiple concurrent agents have been used in cancer therapeutics with good results.

When testing multiple neuroprotective agents concurrently in phase II, statistical designs can include periodic data analysis and aggressive prespecified definitions for discontinuing an agent if it seems futile. For example, a statistical model could be adopted to stop enrolling in any intervention arm for lack of substantial promise if there is low probability that the treatment difference versus placebo will be greater than a prespecified threshold (example, 5%) for the primary end point. This type of aggressive trial design takes on a low risk of stopping a potentially effective agent, but also has a higher probability of eliminating early a truly nonpromising agent. Dropping an agent from further enrolment can allow the study to focus on the remaining agents or introduce a different agent into the study. The ultimate goal of this type of adaptation would be to end the study with ≥1 agents that have remained promising enough to test in a phase 3 trial.

Conclusions

The dismal past of neuroprotection for acute ischemic stroke may now be replaced by a promising future based on novel treatment approaches and clinical trials. Neuroprotection with pharmacological and nonpharmacological therapies can be envisioned to maintain the ischemic core and extend the time window of beneficial reperfusion. Neuroprotection may also ameliorate reperfusion injury to further improve outcome from recanalization therapies. Clinical trials to prove the benefits of neuroprotection before, during, or after reperfusion will require novel trial designs.

Disclosures

None.

References


KEY WORDS: neuroprotection  reperfusion  reperfusion injury  secondary prevention  thrombectomy