

Neuroprotection as an Adjunct to Mechanical Thrombectomy

Finding the optimal combination to preserve brain and provide better outcomes.

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Currently, the only pharmacologic intervention with demonstrated efficacy in acute ischemic stroke is recombinant tissue plasminogen activator (tPA).¹ This treatment aims to reestablish perfusion in occluded vessels, and although it has proven benefits when given within an early time frame, it comes with the added risk of hemorrhagic conversion.² Furthermore, it is less effective in emergent large vessel occlusions.³ The narrow time frame in which it may be administered limits its use as well.⁴ Once deprived of blood flow, oxygen, nutrients, and a means to clear metabolic byproducts, a core of tissue in the stroke territory dies by necrosis, and a rim of tissue in the penumbra may lie quiescent or progress to death through apoptotic pathways, even after perfusion is restored.

Studies on neuroprotection have targeted this region. By blocking the intermediate steps in programmed cell death, the goal is to preserve salvageable neurons and other cells that might otherwise progress to apoptosis. Despite encouraging results with many different agents in animal models, the benefits have not transferred to the clinical studies where human trials may have failed due to issues with effective drug delivery, timing, and lack of coadministration with effective thrombolysis.⁵ By focusing on these medications as an adjunct to mechanical thrombectomy, as opposed to a stand-alone monotherapy, previously shelved agents and new targets may find new utility in the clinical setting.

NEUROPROTECTIVE AGENTS AND THEIR TARGETS

Metabolic failure from the abrupt loss of energy-providing substrates leads to neuronal death through mass excitotoxicity. Failure of adenosine triphosphate-dependent

ion pumps leads to membrane depolarization from an influx of calcium and sodium ions, and widespread excitatory neurotransmitter release (notably glutamate) ensues, exacerbating this phenomenon. The increase in intracellular calcium ions activates proapoptotic proteins such as caspases that promote cell breakdown and apoptosis.⁶ Reactive oxidative species are produced, which further degrade the neurons' structural integrity through lipid peroxidation and membrane perforation. Activation of inflammatory pathways and subsequent cytokine release, along with the release of matrix metalloproteinases that disrupt endothelial tight junctions and break down the blood-brain barrier, promote neutrophil recruitment from the circulation, perpetuating the cycle of further cellular breakdown and oxidative agent release (Figure 1).

Neuroprotective agents selected to inhibit each of these pathways have been examined in humans and brought to the bedside on the strength of numerous laboratory studies showing clear efficacy in animal models of stroke. Time after time, discouraging results showed no clear benefit in human stroke patients who received neuroprotective drugs compared to those receiving standard therapy. Many theories have been posited to explain this; foremost is the idea that animal models for stroke are poor comparisons to human models. Lab animals lack genetic variability, phenotypic heterogeneity, and medical comorbidities that human stroke trial cohorts have by nature. In animal models, strokes are created in a controlled fashion with a well-defined "time zero" and a relatively consistent stroke territory. This degree of homogeneity facilitates close study of the mechanism, as well as how a single condition change can

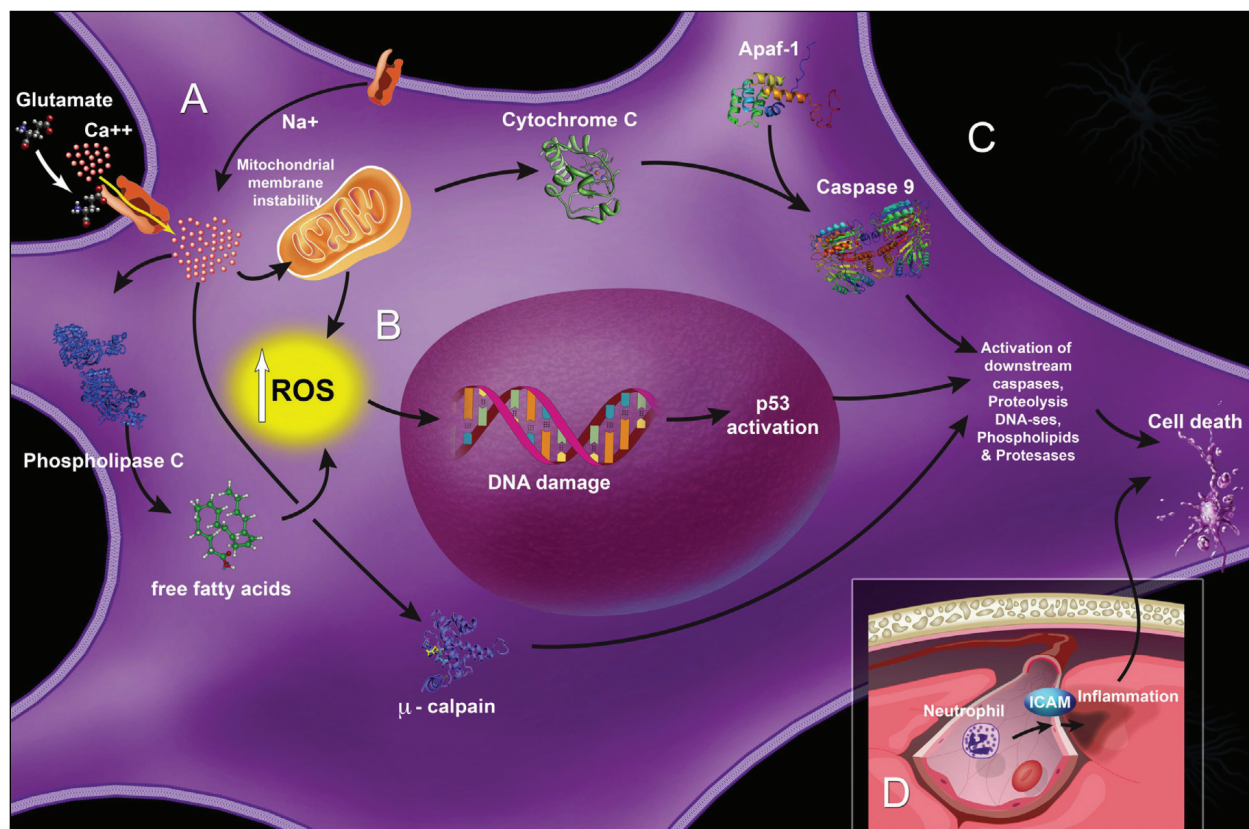


Figure 1. Illustration of cell-signaling cascades and mechanisms of ischemia targeted by clinically evaluated neuroprotective agents. Glutamate-mediated sodium and calcium channel activation results in depolarization and activation of cascades, leading to apoptosis, targeted by inhibitors of ligand binding or direct blockade of the channels (A). Production of reactive oxidative species (ROS) can lead to DNA damage and trigger downstream cell death mechanisms (B). Administration of neurotrophic and vasoactive agents may modify the extracellular matrix (C) and has shown promise in the treatment of cerebral infarcts in rats. Neutrophil-mediated inflammatory changes have been associated with brain injury in ischemia (D), and antibodies designed to target cell surface receptors on neutrophils and endothelial cells have been studied in order to prevent infiltration of these cells into the ischemic bed and subsequent downstream oxidative damage. Reprinted from Clin Neurol Neurosurg, 129, Grupke SL, Hall J, Dobbs M, et al, Understanding history, and not repeating it. Neuroprotection for acute ischemic stroke: from review to preview, 1–9, Copyright (2015), with permission from Elsevier.

alter stroke. Time to treat is also relatively uniform in animal studies but can vary from hours to days in human trial patients. Importantly, many animal models for stroke are based on physical blockage of a cerebral vessel for a uniform period of time, after which, the obstruction is removed and the stroke bed is reperfused.

It has been shown that neuroprotective drugs are more effective and the treatment window is extended in the setting of reperfusion.⁷ Even in permanent occlusion models, animals used in these studies typically have better collateral circulation to their stroke territory than their human counterparts. This is not a luxury that human patients shared in any reliably reproducible fashion in previous trials, and as such, the bioavailability

of these study drugs to the infarcted area of interest has to be questioned. In the human patient, these oral and intravenously administered drugs are needed at a precise location behind a vascular obstruction. This is where the interventionist has a current and future role.

MECHANICAL THROMBECTOMY AS A SETTING FOR NEUROPROTECTIVE THERAPY

At the time of the previously mentioned clinical trials, mechanical thrombectomy was not uniformly implemented in acute emergent large vessel occlusion. It represented a niche intervention with narrow treatment windows, which, like tPA, meant it was not used in a majority of stroke patients. However, since early 2015,

there has been a sea change in neuroendovascular treatment of acute ischemic stroke after several prospective studies demonstrated clear superiority of endovascular intervention over conventional best medical care.⁸⁻¹² This presents a unique opportunity—the practitioner has never had direct access to the vasculature beyond an acute occlusion in a large preselected cohort of patients. After what is now standard treatment, the interventionist is left with a reperfused penumbra and a conduit through which to directly administer a drug (or cocktail of drugs) to this area. This territory is rife with tissue that may have already started down a biochemical cascade toward apoptosis, even after achieving recanalization and reperfusion. This represents an optimal moment to remedy most of the problems presented in previous human trials of neuroprotective medications—the doubt with regard to bioavailability is resolved as the agent is delivered superselectively via a microcatheter directly to the target, and the potential for systemic side effects is minimized. The catheter system to administer the drug is already in place from the thrombectomy, so there is minimal additional mechanistic risk. The patient base more closely mirrors many animal models of the past 3 decades, with reperfusion prior to drug administration. Some heterogeneity in the patient population is offset, as all patients would be, by virtue of being deemed appropriate for thrombectomy, all afflicted with a large vessel occlusion and treated within a narrow time window.

ANIMAL EXPERIMENTS AND EARLY CLINICAL TRIALS

Recently, an animal model has been developed to recreate the scenario of thrombectomy and intra-arterial drug administration in the lab.¹³ Briefly, a mouse is sedated and the carotid bifurcation and middle cerebral artery (MCA) are surgically exposed. The distal external carotid artery (ECA) is permanently occluded, and the internal carotid artery (ICA) and MCA are temporarily clamped for 1 hour. After allowing for 5 minutes of reperfusion through the ICA and MCA, a study agent or saline control is injected into the ECA.

In the first study using this model, the neuroprotective agent chosen was verapamil. This is an L-type calcium channel blocker with the same mechanism of action of previously studied potentially neuroprotective drugs,¹⁴ but it has the added benefit of a long track record of safe intra-arterial administration, as intra-arterial infusion is currently used to treat cerebral vasospasm.¹⁵ With a narrow side effect profile, a proven history of feasibility and safety, and a logical means through which the apoptotic pathway may be interrupted, this drug was infused into the stroke bed, and animals were tested behaviorally for 1 week afterward. Mice that received the therapy scored significantly better on a motor function test than their counterparts in the control group, and histologic testing for stroke volume 7 days after stroke showed a significantly smaller region of infarct in the treated group (Figures 2 and 3).¹⁶

Although still in the early stages, these findings point to a potentially exciting and important new tool in the interventionist's armamentarium. Dozens of drugs previously tested in humans (and an order of magnitude more examined in the laboratory) are relevant again. The ongoing SAVER-I trial (NCT02235558) is the first phase 1 trial to convert bench-to-bedside translational intra-arterial therapy. The ESCAPE-NA1 trial (NCT02930018) is evaluating intravenous administration of NA-1 (NoNO Inc.), an agent that enhances resistance to ischemia by uncoupling glutamate-mediated neurotoxic signaling pathways,^{17,18} in patients undergoing thrombectomy. ENIS I (NCT02831088) is evaluating stroke patients

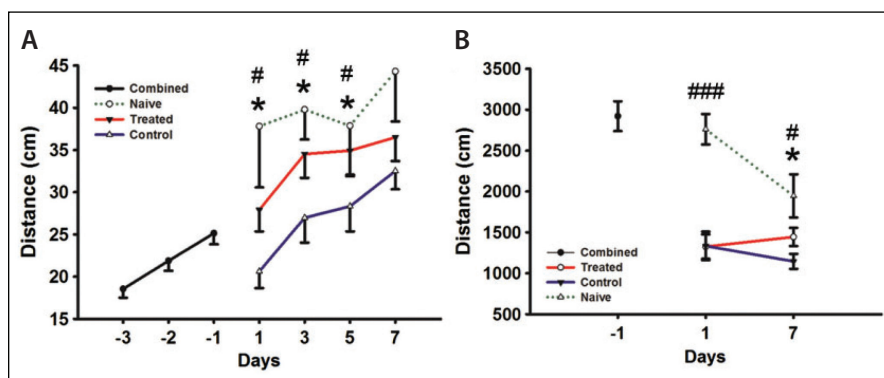


Figure 2. Behavioral measurements for rotor rod and open field for combined (black), naive (green dashed), treated (red), and control (blue) groups. Rotarod forced motor movement test for combined groups to learn a task on days -3, -2, and -1; groups were separated following stroke surgery into control, treated, and naive groups and were tested on days 1, 3, 5, and 7 (A). Open field free roam movement for combined groups on day -1 and separated into control, treated, and naive groups on days 1 and 7 (combined, N = 49; treated, n = 25; control, n = 20; naive, n = 5) (B). Asterisk (*) indicates $P < .05$ for treated versus control; hash (#) indicates $P < .05$ for naive versus control; and triple hash (###) indicates $P < .001$ for naive versus control and treated. From Maniskas ME, Roberts JM, Aron I et al, *J Cereb Blood Flow Metab* (36, 4), pp. 721–730, copyright © 2016, reprinted by Permission of SAGE Publications, Ltd.

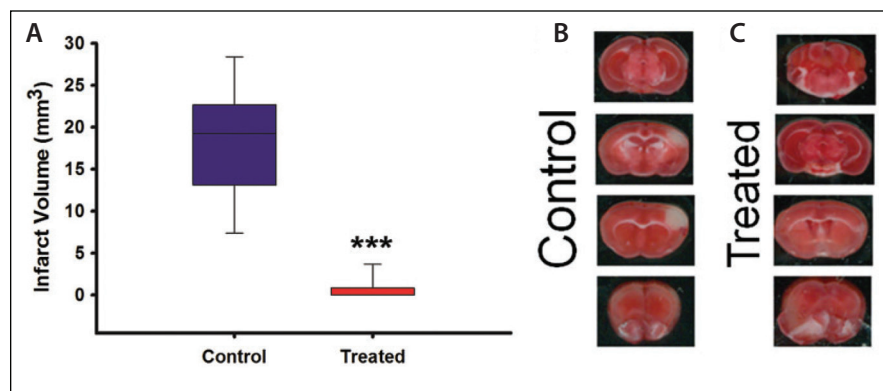


Figure 3. Infarct volume analysis for control versus treated groups using triphenyl-tetrazolium chloride (TTC) and cresyl violet–stained stroked tissue (treated, n = 18; control, n = 15) (A). TTC image for the control group (B). TTC image for the treated group (C). Triple asterisk (***) indicates $P = .001$. From Maniskas ME, Roberts JM, Aron I, et al, *J Cereb Blood Flow Metab* (36, 4), pp. 721–730, copyright © 2016, reprinted by Permission of SAGE Publications, Ltd.

who undergo thrombectomy and subsequently receive an infusion of Neu2000 (GNT Pharma), a drug that both inhibits methyl-D-aspartate receptor–mediated excitotoxicity and acts as a free radical scavenger.¹⁹

Although these studies will not employ intra-arterial treatment, they will be an important look at neuroprotection in blinded trials where recanalization is documented in all patients. If these studies recreate the clinical benefits in patients that researchers have seen in animal studies for years, it is easy to envision superselective intra-arterial infusion of a synergistic combination of neuroprotective drugs as becoming standard of care in acute stroke care in the future. This provides an opportunity for the interventionist to assume a role in the research, study, and development of pharmacologic therapies for acute stroke. An analogous situation to our involvement in product and device development, this allows us to provide our perspective and insight to ultimately hone therapies that preserve brain and improve patient outcomes. ■

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