Neuroprotective delivery platforms as an adjunct to mechanical thrombectomy

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Despite the success of numerous neuroprotective strategies in animal and preclinical stroke models, none have effectively translated to clinical medicine. A multitude of influences are likely responsible. Two such factors are inefficient recanalization strategies for large vessel occlusions and suboptimal delivery methods/platforms for neuroprotective agents. The recent endovascular stroke trials have established a new paradigm for large vessel stroke treatment. The associated advent of advanced mechanical revascularization devices and new stroke technologies help address each of these existing gaps. A strategy combining effective endovascular revascularization with administration of neuroprotective therapies is now practical and could have additive, if not synergistic, effects. This review outlines past and current neuroprotective strategies assessed in acute stroke trials. The discussion focuses on delivery platforms and their potential applicability to endovascular stroke treatment.

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KEY WORDS acute ischemic stroke; mechanical thrombectomy; neuroprotection

To date, few effective therapies exist for treatment of acute ischemic stroke (AIS).2,3,4,5,7,75 In select individuals, intravenous tissue plasminogen activator (tPA) improves outcomes when administered within 4.5 hours of symptom onset.37 Limitations of intravenous thrombolysis have led to the development of alternative recanalization and reperfusion strategies.11,77,78 The 2015 endovascular stroke trials demonstrate that the prompt use of new-generation mechanical thrombectomy devices, particularly stent retrievers, significantly improves functional independence in the setting of large-vessel stroke compared with best medical management alone.14,17,33,48,81,92 These trials marshaled a new treatment paradigm that has revolutionized acute stroke care. A greater number of stroke patients are now eligible for established therapies with potential for substantially improved functional outcomes. However, significant limitations exist with regard to prehospital management, timely selection for intravenous tPA or endovascular therapy, and multidisciplinary coordination of posttreatment stroke and ICU care.4,6 Perhaps most importantly, both intravenous thrombolysis and mechanical revascularization target vessel recanalization rather than tissue reperfusion and are highly dependent on time.

Despite recent advances, the rates of functional independence (14%—58%) following mechanical thrombectomy are poor compared with the efficient rates of recanalization (60%—90%).2,34 The mechanism underlying this paradox remains elusive. One hypothesis, first proposed in the cardiology literature, is the “no-reflow phenomenon.” Supporters advance the concept of minimal capillary reperfusion despite adequate recanalization.28 Restoration of blood flow is thought to alter the microvascular milieu, creating a proinflammatory state that renders affected microvascular beds incompetent.21,72,98 While blood flows through the large vessels, there is resistance at the capillary level. A lack of functional reperfusion causes marginally viable penumbral tissue to be recruited into the ische-
mic core. The discrepancy between recanalization rates and functional outcome underscores the need for further advancements in stroke therapy.

Endovascular treatment is recommended in appropriately selected patients who have symptom onset within 6 hours of presentation. However, The International Management of Stroke (IMS III) trial found that for every 30-minute delay in the time to reperfusion, there was a 12%–15% relative reduction in the likelihood of good clinical outcome. Not only is the time window for revascularization short, there is a bias toward better outcome earlier in the treatment period. As thrombectomy devices and recanalization rates have improved significantly, alternative points along the stroke treatment pathway must now be engaged to improve outcomes. Extension of the treatment window by preserving “at-risk” brain tissue is a logical target.

Adjunct neuroprotective administration in the setting of mechanical revascularization could address these therapeutic gaps. Neuroprotective agents may promote reperfusion at the capillary level in the region of the target tissue and could potentially increase the time window for effective recanalization (by preserving brain tissue and decreasing hemorrhage rates). New-generation mechanical thrombectomy delivery systems provide a unique opportunity to effectively administer neuroprotectants in the treatment of AIS. This review focuses on neuroprotective strategies and their potential ability to “freeze time” by limiting ischemic damage while a patient proceeds through the acute stroke pathway. The Discussion introduces novel platforms for delivery of neuroprotective therapies and specifically highlights the potential utility of neuroprotection as an adjunct before, during, and after mechanical thrombectomy.

Barriers to Implementation of Neuroprotective Strategies

Thousands of preclinical animal studies have demonstrated benefits of neuroprotective therapies in the setting of experimental acute stroke. However, none of these treatment strategies have been widely translated to human patients. Species-specific differences in brain structure and function, lack of sex heterogeneity, and a shortage of trials in the setting of relevant comorbidities are potential reasons for translational failures. The Stroke Treatment Academic Industry Roundtable (STAIR) recommendations were created in an effort to develop a rigorous standard in the transition of preclinical neuroprotectant studies to clinical trials.

Factors that limit the potential for treatment agents to reach target territories (ischemic penumbra) can prevent significant changes in clinical stroke outcomes even if neuroprotective therapies could otherwise salvage ischemic tissue. Such factors include lack of perfusion due to thrombus burden, inefficient delivery methods, and poor collateral vessels. In the past, neuroprotectant delivery platforms were tailored and optimized to supplement definitive revascularization strategies, such as endovascular therapy. Mechanical revascularization presents a now-proven procedure with no potential drug-drug interactions that can be administered in series or parallel with neuroprotective agents. This combined, and potentially synergistic, therapeutic strategy holds great promise.

The sections below outline the various time points, with respect to mechanical thrombectomy treatment, at which putative neuroprotective agents may be administered.

Prehospital Delivery Methods

In AIS, the volume of the ischemic core expands into previously salvageable penumbral tissue as time progresses. A slower rate of early diffusion-weighted imaging (DWI) growth is associated with greater penumbral salvage following tissue reperfusion. Neuroprotective strategies could slow the rate of ischemic growth prior to endovascular AIS treatment (Table 1). Successful application would broaden eligibility for endovascular therapy and ultimately improve functional outcomes for each patient by shifting the time-to-reperfusion/functional outcome curve. The Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial was the first to deliver a neuroprotective agent during the hyperacute period, the “golden hour” after stroke onset. Although FAST-MAG did not achieve its primary efficacy endpoint (that prehospital administration of magnesium sulfate during the hyperacute phase of AIS would reduce disability at 90 days), it established safety and feasibility of a novel prehospital delivery platform. The investigators demonstrated that a study agent could be effectively delivered to patients during the first 60 minutes after stroke onset by ambulance paramedics and established methods and protocols that can be used in future trials. An under-recognized, yet important aspect of the trial was the implementation of a 2-stage screening process that paramedics used to identify potential study patients. The first stage consisted of assessment via the Los Angeles Prehospital Stroke Screen (LAPSS). This is a diagnostic inventory that takes minutes to perform, exhibits high sensitivity and specificity, and is widely used among ambulance personnel worldwide. The second stage incorporated physician assessment over the telephone. These streamlined steps allow neuroprotective agents to be safely administered while patients were delivered to the hospital (parallel processing). In a subset analysis, investigators studied patients who received prehospital treatment with magnesium or placebo initiated less than 2 hours from symptom onset and underwent endovascular treatment. Magnesium therapy still showed no effect; however, the investigators calculated that the strategy exposed patients to 3 hours and 28 minutes of potential neuroprotective exposure prior to endovascular treatment.

An in-depth discussion of novel neuroprotective agents amenable to this type of delivery mechanism is beyond the scope of this paper. However, there are a number of promising therapies, such as NA-1, glyburide, activated protein C, and uric acid, that have recently passed Phase 2 clinical trials.

It is hypothesized that the failure of many neuroprotective strategies is due to the fact that agents only target 1 point in a mechanistic pathway. Hypothermia, however, is a promising therapy that exhibits a wide range of cel-
Neuroprotection and mechanical thrombectomy

Systemic cooling to a temperatures of 32°C and 34°C for 24 hours has been shown to increase survival and improve neurological outcome in patients with spontaneous circulation restoration after cardiac arrest due to ventricular fibrillation. Induced hypothermia was first found feasible and safe in acute ischemic stroke in the Cooling for Acute Ischemic Brain Damage (COOL AID) open pilot study. EuroHYP-1 is an ongoing Phase 3 clinical trial that employs systemic cooling to decrease body temperature to a target between 34°C and 35°C. Hypothermia is initiated within 6 hours of stroke onset and maintained for 24 hours. The primary outcome is the modified Rankin Scale (mRS) score at 90 days.

Remote ischemic perconditioning (preconditioning) (rPerC) has been shown to be neuroprotective in animal models of cerebral ischemia. rPerC occurs when ischemia induced in one organ leads to ischemic tolerance in others, with the protective effect attributed to the activation of multiple endogenous defense mechanisms. The safety of rPerC was tested in a randomized single-center study in patients with myocardial infarction. The treatment was found to be safe and effective in myocardial salvage.

### TABLE 1. Prehospital delivery methods

<table>
<thead>
<tr>
<th>Reference/Registration No.</th>
<th>Study Name</th>
<th>Study Type</th>
<th>Neuroprotectant/Neuroprotective Mode</th>
<th>Treatment Method</th>
<th>Primary Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Saver et al., 2015</td>
<td>FAST-MAG</td>
<td>RCT</td>
<td>Magnesium sulfate</td>
<td>IV w/in 45 mins of stroke symptoms</td>
<td>mRS score at 90 days</td>
<td>Prehospital infusion of magnesium sulfate was safe w/in 2 hours of stroke symptoms but did not improve disability outcome at 90 days</td>
</tr>
<tr>
<td>Krieger et al., 2001</td>
<td>COOL AID</td>
<td>Open pilot study</td>
<td>Hypothermia (32°C)</td>
<td>Systemic hypothermia w/in 6.2 ± 1.3 hrs</td>
<td>Safety &amp; feasibility of moderate hypothermia</td>
<td>Induced hypothermia found to be safe w/ mRS score of 3.1 ± 2.3 at 3 mos</td>
</tr>
<tr>
<td>van der Worp et al., 2014</td>
<td>EuroHYP-1</td>
<td>RCT</td>
<td>Hypothermia (34°C–35°C)</td>
<td>Intravenous infusion of 20 ml/kg refrigerated normal saline (4°C) over 30–60 mins or a surface cooling method</td>
<td>mRS score at 90 days</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT01584167</td>
<td>iCOOL2</td>
<td>RCT</td>
<td>Hypothermia</td>
<td>EMCOOLS Flex.Pads</td>
<td>Change in brain temperature during 1 hr after start of cooling</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Meng et al., 2012</td>
<td></td>
<td></td>
<td>Upper-limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis</td>
<td>Prospective randomized study</td>
<td>Repetitive bilateral-arm ischemic preconditioning</td>
<td>5 brief cycles of bilateral upper-limb ischemia, twice daily for 300 consecutive days</td>
</tr>
<tr>
<td>Hougaard et al., 2014</td>
<td>Remote Ischemic Perconditioning as an Adjunct Therapy to Thrombolysis in Patients With Acute Ischemic Stroke</td>
<td>Open-label blinded outcome proof-of-concept study</td>
<td>rPerC</td>
<td>Prehospital rPerC as an adjunct to treatment w/ intravenous alteplase.</td>
<td>Penumbral salvage as defined by the vol of the perfusion-diffusion mismatch not progressing to infarction after 1 mo</td>
<td>rPerC reduced tissue risk of infarction using voxel-wise analysis after adjustment for baseline perfusion &amp; diffusion lesion severity</td>
</tr>
<tr>
<td>Pico et al., 2016</td>
<td>RESCUE BRAIN</td>
<td>RCT</td>
<td>rPerC</td>
<td>rPerC w/in 6 hrs of stroke onset</td>
<td>Absolute difference in brain infarct volume measured by DWI MRI from baseline to 24 hrs</td>
<td>Ongoing</td>
</tr>
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</table>

IV = intravenous; RCT = randomized clinical trial.
Bilateral-arm rPerC was first found to be neuroprotective in reducing the incidence of stroke and transient ischemic attack in patients with symptomatic intracranial arterial stenosis.64 rPerC was then tested as an adjunct to thrombolysis in patients with acute ischemic stroke in an open-label, prehospital, paramedic-administered study.44 This study used MRI lesion volumes (as opposed to functional outcomes) to determine effect size. Upper-arm rPerC was performed for a total of 4 cycles by ambulance staff and was discontinued on arrival to the stroke unit. The study showed no overall benefit. However, when the findings were adjusted for baseline severity of hypoperfusion, a voxel-by-voxel analysis showed increased tissue survival after 1 month in the treatment group. This suggests that prehospital rPerC may have neuroprotective capacity. Currently, the Remote Ischemic Conditioning in Acute Brain Infarction (RESCUE BRAIN) trial is underway. This study examines whether rPerC during ischemic stroke (< 6 hours) reduces brain infarct size at 24 hours.73 The primary end point is the absolute difference in brain infarct volume measured by DWI MRI from baseline to 24 hours, in the intervention versus control groups. The authors state that if RESCUE BRAIN shows effect on infarct volume, they would conduct a larger trial using a clinical primary end point. In the setting of acute stroke, rPerC is a promising prehospital neuroprotective adjunct to mechanical thrombectomy. The treatment is easy to administer and has already demonstrated positive results in patients with myocardial infarction and those with symptomatic intracranial stenosis.

**Neuroprotectant Administration Coupled With Mechanical Thrombectomy**

Activated protein C (APC) is a promising neuroprotectant agent. APC is an endogenous serine protease that is generated in multiple cell types within the neurovascular unit during the response to cerebral ischemia.35,99 Like hypothermia, APC targets several pathological mechanisms of the ischemic cascade. The Safety Evaluation of 3K3A-APC in Ischemic Stroke (RHAPSODY) Phase 2 clinical trial is assessing the safety, pharmacokinetics, and preliminary efficacy of multiple increasing intravenous doses of 3K3A-APC (recombinant variant of human APC) in combination with tPA, mechanical thrombectomy or both (registration no. NCT02222714). Although the neuroprotectant delivery route is intravenous, this is the first trial of its kind to incorporate mechanical thrombectomy with the use of a putative neuroprotectant. Just as the FAST-MAG trial set the stage for prehospital delivery of neuroprotectants, the RHAPSODY trial has established the use of mechanical thrombectomy with the concurrent administration of neuroprotective agents.58 The study authors needed to develop criteria that ensured patients are treated with current evidence-based standards for mechanical thrombectomy while, at the same time, allowing for assessment of efficacy for a neuroprotective agent. The door-to-needle times, imaging criteria, and National Institutes of Health Stroke Scale (NIHSS) scores established for inclusion in this study will set the standard for future investigations for combined neuroprotective agents and mechanical thrombectomy procedures (Table 2).

The Safety and Efficacy of NA-1 in Patients With Iatrogenic Stroke After Endovascular Aneurysm Repair (ENACT) study established safety and feasibility of neuroprotective strategies in the setting of endovascular procedures.40 ENACT was a double-blind, randomized, controlled trial that found that NA-1 could be safely administered to patients undergoing endovascular repair of ruptured and unruptured intracranial aneurysms. Investigators assessed whether NA-1 reduced the volume and number of iatrogenic ischemic strokes (detection via MRI). NA-1 was administered at the conclusion of the procedures and was found to reduce the number of iatrogenic embolic strokes but not the overall volumes of

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</tr>
</thead>
<tbody>
<tr>
<td>NCT02222714; Lyden et al., 2016</td>
<td>Safety Evaluation of 3K3A-APC in Ischemic Stroke (RHAPSODY)</td>
<td>RCT</td>
<td>APC</td>
<td>Safety &amp; efficacy of multiple increasing intravenous doses of 3K3A-APC in combination w/ tPA, mechanical thrombectomy or both</td>
<td>Adverse events that meet dose-limiting toxicity criteria</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Hill et al., 2012</td>
<td>The Safety and Efficacy of NA-1 in Patients With Iatrogenic Stroke after Endovascular Aneurysm Repair (ENACT)</td>
<td>RCT</td>
<td>NA-1</td>
<td>IV infusion of NA-1 after endovascular aneurysm repair</td>
<td>Safety as well as no. &amp; vol of new ischemic strokes defined by MRI at 12–95 hrs after infusion</td>
<td>NA-1 group sustained fewer ischemic infarcts than placebo group as measured by DWI &amp; FLAIR</td>
</tr>
<tr>
<td>NCT02930018</td>
<td>The Safety and Efficacy of NA-1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1)</td>
<td>RCT</td>
<td>NA-1</td>
<td>NA-1 use coupled w/ endovascular revascularization in patients w/ small established infarct core &amp; w/ good collateral circulation</td>
<td>mRS score at 90 days</td>
<td>Ongoing</td>
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lesions. This study establishes feasibility of intravenous delivery of a putative neuroprotective agent during neuroendovascular procedures. The investigators have leveraged their delivery platform to test the same agent in AIS. The Safety and Efficacy of NA-1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) Phase 3 clinical trial expands the use of NA-1 to patients with major AIS (registration no. NCT02930018). AIS patients with a small, established infarct core and favorable collateral circulation are treated with a single 2.6-mg intravenous dose of NA-1 or placebo once selected for mechanical thrombectomy. The primary study outcome is global disability, with secondary measures of functional dependence, neurological outcome, activities of daily living, and mortality rate.

**Intraarterial Neuroprotectant Delivery**

Inadequate delivery of neuroprotective therapies to target tissue has been a concern in the setting of emergent large vessel occlusion. A large thrombus prevents the direct passage of blood, oxygen, nutrients, and any systemically administered agents. It is postulated that potential neuroprotectants reach the penumbral tissue through collateral circulation. New-generation endovascular techniques allow for selective intraarterial drug delivery, a concept first described as endovascular restorative neurosurgery. Neuroprotective agents can be administered regionally through guide catheters positioned in the carotid or vertebral artery. Alternatively, treatments can be administered directly through microcatheters positioned at the face of, or beyond, the occlusive lesion. The benefits of intraarterial delivery of neuroprotectants are numerous. A high concentration/dose ratio can be achieved in a small, targeted volume of the brain, ultimately leading to lower systemic toxicity. Delivery can be executed rapidly and accessed repeatedly, while limiting perturbations of neural tissue inherent to traditional surgical routes of access.

The neuroendovascular community has a significant experience with intraarterial delivery platforms outside of stroke treatment. Lessons from these endeavors can be translated directly to mechanical thrombectomy procedures. Isolated or daily intraarterial infusion of spasmylolytic agents (papaverine, verapamil, nitroglycerine) is common practice in the setting of cerebral vasospasm. Continuous intraarterial infusion of nimodipine has recently been reported. Safety of active infusion over the duration of 2 weeks was documented. The safety of continuous intraarterial infusion of nimodipine has implications for the delivery of neuroprotectants. Current trials (see below) use short-term, intraoperative, administration of neuroprotective agents. However, with the advent of continuous intraarterial treatment, the delivery of neuroprotectants can, theoretically, be administered safely for longer durations after stroke.

Intraarterial delivery of chemotherapeutics for brain tumors was first described in the 1950s. With the advancement of endovascular techniques, the concept of superselective intraarterial cerebral infusion was established. This allows for the selective targeting of afferent tumor vessels, enabling the infusion of a chemotherapeutic agent to a localized area. Selective microcatheter delivery of a targeted agent to brain tumors was first described in 2009. To date, superselective intraarterial cerebral infusion has been successfully leveraged for the treatment of high-grade gliomas and retinoblastomas.

In large-vessel stroke, intraarterial delivery of neuroprotectants can occur prior to, or following, clot extraction. If an agent is delivered distal to a thrombus prior to recanalization, it will likely remain in the tissue bed until flow is restored. This has implications on both efficacy and toxicity. However, if the neuroprotectant therapy is delivered after recanalization, the agent will be subject to the same first-pass effects that might be seen in other tissue beds. Stent retriever catheters allow for distal delivery once a thrombus is traversed, while aspiration with distal catheters would only allow local/regional administration, as they do not typically cross the face of the clot. Several ongoing trials are examining intraarterial delivery platforms in the setting of acute stroke (Table 3). The Intra-arterial Magnesium Administration for Acute Stroke trial examines the effect of intraarterial high concentration magnesium administration in patients with AIS (registration no.

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<tr>
<td>NCT01502761</td>
<td>Intra-arterial Magnesium Administration for Acute Stroke</td>
<td>RCT</td>
<td>Magnesium</td>
<td>Intraarterial high-concentration magnesium administration</td>
<td>Magnesium concentration in region of cerebral ischemia</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT02235558</td>
<td>Superselective Administration of Verapamil During Recanalization in Acute Ischemic Stroke (SAVER-I)</td>
<td>RCT</td>
<td>Magnesium</td>
<td>Intraarterial verapamil administered immediately following intraarterial thrombolysis (either IPIA or mechanical thrombectomy)</td>
<td>Presence or absence of intracranial hemorrhage</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT02912663</td>
<td>Magnesium and Verapamil After Recanalization in Ischemia of the Cerebrum: a Clinical and Translational Study (MAVARIC)</td>
<td>RCT</td>
<td>Magnesium &amp; verapamil</td>
<td>Selective intraarterial administration of verapamil &amp; magnesium immediately after mechanical thrombectomy</td>
<td>Presence or absence of intracranial hemorrhage</td>
<td>Ongoing</td>
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This study and feasibility study is the first to directly quantify levels of neuroprotectants in the region of ischemia. Similarly, Superselective Administration of Verapamil During Recanalization in Acute Ischemic Stroke (SAVER-1) examines the safety of verapamil as a neuroprotective agent administered intraarterially immediately following intraarterial thrombolysis (either tPA or mechanical thrombectomy) (registration no. NCT02235558). This study uses a new generation mechanical thrombectomy device, and it uses a guide in the region previously burdened by a clot, administering 10 mg verapamil/20 ml of normal saline over 20 minutes. By assessing 2 neuroprotective agents with relatively benign safety profiles, these 2 studies have established a paradigm for administering other intraarterially delivered neuroprotectants.

The Magnesium and Verapamil After Recanalization in Ischemia of the Cerebrum: a Clinical and Translational Study (MAYVARIC) is a Phase 2 clinical trial investigating the safety and feasibility of superselective intraarterial administration of verapamil and magnesium immediately after mechanical thrombectomy (registration no. NCT02912663); 10 mg verapamil/10 ml normal saline and 1000 mg magnesium sulfate/20 ml normal saline are administered over 20 minutes using a microcatheter into vessels that were previously obstructed by thrombus. Outcome measures include symptomatic intracranial hemorrhage and systemic side effects.

Stem cells have been delivered via intraarterial platforms in many clinical stroke trials. Although stem cells are neuroregenerative, rather than neuroprotective, their intraarterial delivery is worth considering in this discussion. At this time, the optimal mode of stem cell delivery (intracerebral, intraventricular, subarachnoid, intraarterial, intraperitoneal, intravenous, and intranasal) remains unclear. However, the intraarterial route has shown promise. Battistella et al. first assessed the use of autologous bone marrow mononuclear cells (BM-MNCs) in 6 patients with nonacute middle cerebral artery (MCA) stroke within 90 days of symptom onset. A large inner diameter microcatheter (SL 1018 Boston Scientific, Target Therapeutics) was used to infuse the stem cells for approximately 10 minutes into the M1 portion of the MCA. As the trial did not include a control group, efficacy could not be ascertained. However, the study did demonstrate feasibility and safety. Another Phase 1–2 clinical trial aimed to assess the safety, feasibility, and effect of BM-MNC transplantation in subacute MCA stroke. BM-MNCs were injected into the M1 segment of the affected MCA region at low pressure 5–9 days after stroke. Once again, the authors found that intraarterial transplantation of BM-MNCs in subacute MCA stroke is feasible and safe. Using similar delivery methods, another BM-MNC trial demonstrated a 40% rate of good clinical outcome (mRS score ≤ 2) and 30% satisfactory clinical improvement (mRS score of 0 in patients with NIHSS score < 8, mRS score of 0–1 in patients with NIHSS scores of 8–14, or mRS scores of 0–2 in patients with NIHSS score > 14) in their study population.

**Alternative Endovascular Delivery Methods**

We previously described the potential benefits of intravenous cooling during AIS. This strategy has been extended to a direct endovascular approach (Table 4). The Cooling for Acute Ischemic Brain Damage (COOL AID) feasibility trial was the first trial to use triple-looped, helically wound, heat-exchange balloon catheters that were placed in the inferior vena cava via femoral vein access. The investigators found that moderate hypothermia is feasible in the setting of AIS with the aid of an endovascular cooling device. The Intravascular Cooling in the Treatment of Stroke (ICTuS) trial expanded on this principle. The study demonstrated that endovascular cooling with a proactive antishivering regimen can be accomplished in awake stroke patients. This study employed the use of a heparin-coated flexible metal catheter with a metallic heat transfer surface that facilitates extraction of heat from the blood as it flows by the catheter. Later, the ICTuS–Longer window (ICTuS-L) trial was developed to determine if endovascular catheterization and cooling could be performed safely in patients treated with thrombolytic therapy. The investigators found no bleeding complications in patients who underwent catheterization. However, the ICTuS-L trial demonstrated an increase in risk of pneumonia in patients receiving endovascular cooling. The Phase 2 ICTuS trial confirmed the safety and feasibility of intra-vascular therapeutic hypothermia in patients undergoing...
thrombolytic therapy. The protocol changes implemented to reduce pneumonia risk appeared to have failed; however, the sample size was small.99

**Neuroprotective Delivery Following Mechanical Thrombectomy**

Despite efforts to achieve vessel recanalization and reperfusion, there remains a percentage of patients who are recalcitrant to endovascular therapy and go on to suffer ischemic injury. In principle, inhibition of inflammatory pathways, prevention of excitotoxicity, reduction of apoptosis, and mitigation of the development of vasogenic edema should improve cellular survival in the area of ischemia and surrounding tissue, commonly referred to as secondary brain injury. Unfortunately, many of the pharmacological treatments developed to target these mechanisms have failed to demonstrate reproducible clinical benefit when evaluated in human subjects. Notably, recent trials of erythropoietin70 and progesterone,99 when used to mitigate secondary brain injury resulting from traumatic mechanisms, did not demonstrate any superiority over placebo medication.

One of the more promising agents aimed at preventing secondary brain injury recently evaluated in a Phase 2 randomized clinical trial is a sulfonylurea receptor 1 antagonist (intravenous delivery) (registration no. NCT01794182).51,88,99 Inhibition of this receptor has the potential to reduce the development of vasogenic edema following ischemic stroke, a key mediator of secondary brain injury.94 Its mechanism rests on an understanding of the role of ischemia in the setting of ischemic stroke, and supports further investigation of brain swelling (measured by midline shift) was also reduced by half when compared with placebo. This evidence, along with an excellent safety profile, suggests that Cirara has the potential to dramatically change the treatment of ischemic stroke, and supports further investigation in a Phase 3 trial (Table 5).

The Efficacy and Safety of Neu2000KWL in Treating Acute Ischemic Stroke Receiving Endovascular Therapy (ENIS I) trial is a study examining the safety and efficacy of Neu2000KWL administered before endovascular therapy within 8 hours of symptom onset with 9 consecutive doses. Neu2000KWL is a sulfonylurea receptor 1 antagonist (intravenous delivery) (registration no. NCT01794182).51,88 It combines intravenous drug administration just prior to endovascular therapy with 9 consecutive infusions of Neu2000KWL at 12-hour intervals following mechanical thrombectomy.

Although not classically considered neuroprotectants, multiple treatment strategies/agents (glycemic control,
statins) have been used to decrease infarct volume, mitigate cerebral edema, and improve clinical outcome in the setting of acute stroke. Trials are being designed to specifically assess the efficacy of these therapies in the subset of large vessel occlusions. Most recently, studies have leveraged some of these treatment strategies as adjuncts after mechanical thrombectomy. The use of statin therapy has been established in primary and secondary stroke prevention. Furthermore, statin administration has been shown to improve recovery after AIS. A population-based prospective cohort study found that initiation of new statin therapy (<72 hours after stroke) was associated with improved 7-day survival, along with good functional outcomes at 7 days and 1 year. Statin use initiated within 3 days of stroke hospitalization is strongly associated with improved poststroke survival. By contrast, withdrawal of statin therapy in the hospital was associated with worsened survival. A more recent meta-analysis of observational studies and randomized trials found that statin therapy at stroke onset was associated with improved outcome. The sum of these findings has led investigators to develop clinical trials. The Neuroprotection with Statin Therapy for Acute Recovery Trial (NeuSTART) found that doses of lovastatin up to 8 mg/kg daily for 3 days after AIS was tolerable. NeuSTART2 is currently studying the safety and efficacy of low dose (80 mg daily) and high dose (640 mg daily) statins administered within 24 hours of symptom onset for 3 days (registration no. NCT01976936). The Administration of Statin On Acute Ischemic Stroke Patient Trial (ASSORT) is a Phase 4 clinical trial examining the effect of statin (atorvastatin 20 mg or pitavastatin 4 mg or rosuvastatin 5 mg) initiated for a week after AIS (registration no. NCT02549846).

Hyperglycemia is a common finding in patients with AIS and is associated with larger infarct volumes, poor clinical outcomes, and increased risk of mortality. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is a Phase 3 study examining 1400 hyperglycemic patients who receive either sliding-scale subcutaneous insulin or continuous intravenous insulin for up to 72 hours, beginning within 12 hours of stroke onset (registration no. NCT01369069). The study is powered to detect a 7% absolute difference in favorable outcome at 3 months. This trial is currently ongoing and will help elucidate the proper management parameters for hyperglycemic AIS patients. Another study is examining the effects of Exenatide, a GLP-1 analog. A decreased risk of hypoglycemia may afford an advantage over insulin therapy in the acute management of hyperglycemia in the setting of AIS. Tight glycemic control in AIS is now being leveraged as an adjunct to mechanical thrombectomy in The Intensive Insulin Therapy With Tight Glycemic Control to Improve Outcomes After Endovascular Therapy for Acute Ischemic Stroke clinical trial (registration no. NCT02054429). This study will examine the effects of intensive insulin therapy versus standard glycemic control in nondiabetic patients presenting within 8 hours of ischemic stroke who have undergone mechanical thrombectomy. The primary outcome is the mRS score at 90 days, and secondary outcome is DWI infarct volume.

Conclusions

Acute stroke treatment has undergone a seismic shift over the past 2 years. A period of rapid device development was coupled with expansion in stroke systems of care. Patients with emergent large vessel occlusion are being diverted to endovascular centers more efficiently and undergoing successful mechanical thrombectomy procedures. Functional outcomes are improving. Combination therapies could be the next great advancement: administering neuroprotective agents and mechanical revascularization procedures in series or parallel could potentially increase efficacy and lengthen the treatment window for acute stroke.

Acknowledgments

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References


Disclosures
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Author Contributions
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