

Advances in Emerging Nondrug Therapies for Acute Stroke 2007

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Numerous clinical trials of thrombolytic and neuroprotective drugs for stroke have been conducted over the last 2 decades. The NINDS trial of intravenous tissue plasminogen activator remains the most notable success. Intra-arterial thrombolysis appears promising, but in the absence of phase III clinical trial data, this approach remains investigational. Numerous pharmaceutical drugs targeting 1 or more cell death pathways have failed to show efficacy. Despite failure, these prior attempts have provided insights regarding critical issues such as proper clinical trial design and the need for more rigorous preclinical drug testing in order to improve the translational leap from bench to bedside.

More recently, accumulating data suggest that “non-drug” approaches toward stroke therapy might also provide new opportunities in addition to more traditional pharmaceutical therapies. As testimony to the growing importance of these alternate and sometimes complementary methods, there has been a proliferation of device trials, and the NINDS, through its key ‘Specialized Program of Translational Research in Acute Stroke’ [SPOTRIAS] initiative,¹ has funded trials of therapeutic hypothermia, caffeine, and normobaric hyperoxia, among others. Although this brief survey focuses on emerging gas and device therapies for ischemic stroke, it should be noted that several other ‘non-drug’ approaches, including physiological strategies (eg, hypothermia, glucose regulation), and natural agents (eg, albumin, magnesium), continue to be tested in ongoing trials.

Gases

Increasing brain tissue oxygenation has long been considered a logical stroke treatment strategy. Although initial efforts using hyperbaric oxygen (HBO) chambers were unsuccessful, the realization that early trials had numerous methodological shortcomings has led to a resurgence of interest in hyperoxia.² As a potential treatment, oxygen has distinct advantages over pharmaceutical drugs: it easily diffuses across the blood-brain barrier to reach target tissues, may act via multiple pathways, and high concentrations of oxygen in brain might be well tolerated.

In the past year, several groups have explored normobaric oxygen therapy (NBO, or inhaled high-flow oxygen) because

of its obvious practical benefits. It is widely available, simple to administer, and noninvasive. Recent data suggest that NBO may have rapid effects in stroke and can be started promptly after symptom onset. The results of animal^{3,4} and human⁵ studies suggest that NBO slows down the process of ischemic cell death after stroke. This “stopping the stroke clock” effect may provide an opportunity to extend the time window for thrombolysis.⁶ While most prior studies have shown efficacy in models of transient focal stroke, a new study suggests that NBO may even be protective in permanent cortical ischemia.⁷ Other studies published this past year have started clarifying NBO’s mechanisms. First, although it was believed that NBO (unlike other oxygen delivery methods) does not significantly raise brain tissue oxygen levels, a rodent study using electron paramagnetic resonance showed that NBO restores ‘penumbra’ oxygen to preischemic baseline levels.⁸ Another study using novel 2-D multispectral reflectance imaging and laser speckle flowmetry found that NBO improves cerebral perfusion and oxygenation in ischemic regions and inhibits perinfarct depolarizations.⁹ Serial multivoxel MR spectroscopy suggested that NBO appeared to reduce lactate and preserve *N*-acetyl cysteine levels after stroke.¹⁰ Intermittent hyperoxia has also been shown to induce ischemic preconditioning.¹¹ These mechanistic data provide an emerging scientific rationale for administering NBO to acute stroke patients. A small feasibility study found lower mortality and complication rates in patients with severe middle cerebral artery stroke treated with venturi-mask oxygenation.¹² A double-blind clinical trial of NBO started within 9 hours after symptom onset has been started within the SPOTRIAS network.

Meanwhile, perhaps not surprisingly, animal studies have shown that HBO may be even more potent than NBO.^{7,13,14} Some studies have addressed the controversial issue of whether HBO exacerbates oxidative stress after stroke. An animal study showed that HBO decreases blood-brain barrier damage¹⁵; however, 2 studies including a small Japanese clinical trial found benefit by combining HBO with free radical scavengers.^{16,17} There are now over 40 HBO-related rodent studies, with only a handful published before 2000.² Cumulatively, these studies have significantly advanced our understanding of critical issues such as the therapeutic time

Received November 30, 2007; accepted December 5, 2007.

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(*Stroke*. 2008;39:289-291.)

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.511485

window of HBO and the optimal chamber pressure, and a multicenter HBO trial is being planned. Alternative methods of oxygen delivery are also being explored. Preliminary results of a cardiac ischemia trial show that myocardial damage can be reduced by infusing super-oxygenated solutions directly into the area of ischemia,¹⁸ suggesting the potential utility of this strategy in stroke patients undergoing intra-arterial thrombolysis. Successful results from these hyperoxia trials may ultimately yield a combined therapeutic approach where NBO is started in the field and subsequently combined with HBO, infusion of super-oxygenated solution, or thrombolysis.

Other gas therapies may also prove beneficial. Ohsawa and colleagues showed that hydrogen selectively reduces the toxic hydroxyl radical ($\cdot\text{OH}$) to H_2O , and has antioxidant and antiapoptotic properties that afford neuroprotection in the setting of ischemia/reperfusion injury.¹⁹ In rodents subjected to focal cerebral ischemia-reperfusion, inhaled 2% hydrogen reduced infarct volume, reduced lipid peroxidation and DNA oxidation, and improved neurological function at 1 week. These data support a novel hypothesis that hydrogen might act as a gaseous oxygen radical scavenger that prevents neuronal death. The results of another rodent study suggest that heliox (30% oxygen and 70% helium—a biological inert gas) is more potent than NBO in reducing infarct volumes after transient focal stroke.²⁰ As compared with the control group (30% oxygen/70% nitrogen), NBO-treated rats showed 56% and 70% reduction in total and cortical infarct volumes, and heliox-treated rats showed 87% and nearly 100% reduction of total and cortical infarct volumes. The authors speculate that helium diffuses into mitochondria and facilitates the egress of nitrogen, thereby enhancing mitochondrial uptake of oxygen and restoring cellular energy levels. Finally, anesthetic gases such as xenon have gained attention because of their neurotransmitter-modulating properties and documented neuroprotective effects in brain ischemia.²¹ These emerging gas therapies need further study before human trials can be considered.

Devices

Several therapeutic devices are being tested in multicenter clinical trials. The NeuroThera Laser System is an intriguing device using infrared laser technology to noninvasively deliver energy to the brain. Significant and sustained efficacy has been documented in animal studies^{22,23} and the results of the first clinical trial testing this device have been published.²⁴ The NeuroThera Effectiveness and Safety Trial-1 (NEST-1) was a prospective, double-blind, multicenter trial enrolling 120 patients with moderate neurological deficits enrolled within 24 hours after symptom onset. The active treatment group suggested benefit across several clinical outcome measures throughout the 90-day study period, which is impressive considering the rather delayed time to treatment (mean 16 hours). More information is needed to determine treatment effects on different stroke subtypes and to understand the precise mechanism underlying these effects. At present it is believed that infrared laser therapy stimulates ATP formation within mitochondria in the ischemic penumbra, leading to tissue salvage, inhibition of apoptosis, and

enhanced neurorecovery.²⁵ A larger confirmatory trial (NEST-2) is underway.

Building on the success of the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial,²⁶ several studies have been initiated to evaluate whether transcranial Doppler ultrasound energy can be used to enhance the rates of arterial recanalization either with or without tissue plasminogen activator and with or without microbubble injection during insonation.^{27,28} Ultrasound parameter settings such as the frequency, power, and duration will need to be carefully considered to minimize the risk of brain hemorrhage previously associated with sonothrombolysis.^{29,30} Finally, although the focus of this article is on acute stroke, it should also be noted that there has been considerable progress over the last year with interventional devices aimed at preventing stroke such as carotid artery stents and patent foramen ovale closure and left atrial appendage exclusion devices.^{31–33} Similarly, significant advances have been made in the field of stroke recovery with robotic devices, repetitive transcranial magnetic stimulation,³⁴ and the development of ‘neural interface’ systems that offer hope to patients who remain paralyzed after devastating strokes.³⁵

Summary

While intra-arterial thrombolysis continues to be actively studied and clinical trials of potential neuroprotectants are ongoing, emerging ‘nondrug’ treatment opportunities may provide additional and complementary ways to tackle acute stroke. We now acknowledge that simple measures such as optimal blood pressure and glucose control may be critical in preserving brain tissue after stroke. Recent data suggests that physiological strategies, eg, induced hypothermia and hyperoxia, may be useful adjunctive therapies that extend the time window, safety and efficacy of thrombolysis. Inhaled gases and ‘natural’ agents such as albumin and magnesium offer the promise of neuroprotection without significant risk for brain hemorrhage or neurotoxicity. Devices may have a role in enhancing stroke thrombolysis, preserving ischemic but non-infarcted tissues, and promoting stroke recovery. In the final analysis, no single treatment is likely to be effective for ischemic stroke. A combination of various treatment strategies along with efforts to increase stroke awareness, reduce the time to treatment, and improve general stroke care through the creation of specialized stroke units, are all going to be essential in reducing the enormous global burden of stroke-related death and disability.

Sources of Funding

Supported in part by NIH grants R01-NS51412, R01-NS37074, R01-NS56458, P01-NS55104, P50-NS10828 and P50-NS51343.

Disclosures

None.

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KEY WORDS: acute stroke ■ non-drug therapies ■ therapy