Stroke – Recognition and Treatment

Number of Contact Hours – 2.3

Audience: APRN/RN

Pharmacology Hrs: 0.5

Goals and Objectives

Goals

The goal of this article is to provide widespread and timely evidence-based endorsements on the recognition and current perspective on treatment options of stroke

Objectives

Describe the symptoms of stroke in young individuals

Discuss the various treatment options for stroke

Identify three neuroprotective agents applied in stroke therapy

Discuss the pathophysiology of stroke

Describe the role of neuroprotective agents in stroke

Introduction

Stroke is the third leading cause of mortality and disability in the United States. Ischemic stroke constitutes 85% of all stroke cases. However, no effective treatment has been found to prevent damage to the brain in such cases except tissue plasminogen activator with narrow therapeutic window, and there is an unmet need to develop therapeutics for neuroprotection from ischemic stroke. Studies have shown that mechanisms including apoptosis, necrosis, inflammation, immune modulation, and oxidative stress and mediators such as excitatory amino acids, nitric oxide, inflammatory mediators, neurotransmitters, reactive oxygen species, and withdrawal of trophic factors may lead to the development of the ischemic cascade. Hence, it is essential to develop neuroprotective agents targeting either the mechanisms or the mediators leading to development of ischemic stroke. It is essential to focus on central nervous system agents targeting these biochemical pathways and mediators of ischemic stroke, mainly those that counteract apoptosis, inflammation, and oxidation, and well as glutamate inhibitors which have been shown to provide neuroprotection in experimental animals. All these agents have been shown to improve neurological outcome after ischemic insult in experimental animals *in vivo*, organotypic

brain slice/acute slice *ex vivo*, and cell cultures *in vitro* and may therefore aid in preventing long-term morbidity and mortality associated with ischemic stroke. [1, rank 3]

Stroke in Younger Individuals

Compared with stroke in older adults, stroke in the young has a disproportionately large economic impact by leaving victims disabled before their most productive years. To date, only limited prior public health and research efforts have specifically addressed stroke in the young. Early diagnosis remains challenging because of the lack of awareness and the relative infrequency of stroke compared with stroke mimics. Moreover, the causes of IS in the young are heterogeneous and relatively uncommon, resulting in uncertainties about diagnostic evaluation and cause-specific management. Emerging data have raised public health concerns about the increasing prevalence of traditional vascular risk factors in young individuals, and their potential role in increasing the risk of IS, stroke recurrence, and poststroke mortality. These issues make it important to formulate and enact strategies to increase both awareness and access to resources for young stroke patients, their caregivers, and health care professionals. Given the relative lack of high-level scientific evidence concerning stroke in young individuals, an evidence-based management guideline was considered unfeasible. [2, Rank 5]

Recognition and Differential Diagnosis

Few studies have addressed the reasons for underdiagnosis of stroke in the young. In a single-center analysis of 57 IS patients aged 16 to 50 years, 8 were initially misdiagnosed, including 7 who were initially discharged. Predictors of a missed diagnosis were age younger than 35 years and posterior-circulation stroke. Early (<48-hour) MRI may reduce the rate of misdiagnosis. There is more literature regarding stroke overdiagnosis (false-positives), an important concern given the potential risks of thrombolytic complications in stroke mimics. Approximately 20% to 50% of adults and children with acute stroke-like symptoms will prove to have an alternative diagnosis. The most frequent mimics of IS in young adults and adolescents are seizures, acute vestibular syndrome, migraine, infections, brain tumors, toxic-metabolic encephalopathy (particularly hypoglycemia), hypertensive encephalopathy, gastroenteritis, and conversion disorder. Less frequent sources of misdiagnosis are cardiac events, herpes-simplex virus encephalitis, demyelinating disease, and myasthenia gravis. Among patients treated with IV thrombolysis, the proportion of mimics is lower, between 3% and 13%. Reassuringly, among young patients with stroke (including mimics) treated with IV thrombolysis, there does not seem to be an increased risk of symptomatic ICH. [3, rank 4]

The symptoms of IS in young adults and adolescents are often similar to those in older patients. The diagnosis is straightforward when presented with typical stroke symptoms such as an acute hemiparesis. However, the diagnosis becomes challenging with atypical symptoms. A few salient points are worth highlighting. Right-hemispheric strokes are often

misdiagnosed initially because language is preserved. Nonlocalizing syndromes, including neuropsychiatric symptoms, acute confusional states, and diminished level of alertness, may sometimes be the presenting features. Even small infarcts in the midbrain and thalamus may cause diminished levels of alertness. While strokes usually cause negative symptoms such as weakness, positive symptoms can develop, including unilateral limb-shaking, hemiballismus, or chorea. In patients presenting with dizziness, it is particularly difficult to distinguish stroke from vestibular neuronitis or Ménière disease. There is evidence that the presence of a negative head-impulse test, skew deviation, or direction-changing nystagmus in eccentric gaze has a sensitivity of 100% and specificity of 96% for stroke. Patients should not be dismissed unless they can walk without imbalance. Patients with severe nausea and vomiting due to missed cerebellar infarction may later experience fatal brainstem compression due to swelling, a condition ironically labeled fatal gastroenteritis. Patients presenting with isolated symptoms (e.g., cranial neuropathies, visual symptoms, pure sensory loss, monoparesis) may also be misdiagnosed because these are relatively uncommon. [4, Rank 5]

Several studies have shown an increased risk of stroke in patients with migraine with aura, especially women younger than 45 years, cigarette smokers, and those using hormonal contraception. In migraineurs who present with prolonged focal neurologic symptoms, particularly visual or language disturbance, it can be challenging to distinguish migraine from stroke. The absence of a history of migraine with aura, or a change in the quality of headache, should make one question the diagnosis of migraine. Moreover, sensory changes in migraine usually have a migrating quality, moving over 20 to 30 minutes across parts of the body, whereas stroke-related sensory changes usually occur abruptly. Adolescents and children usually have a headache or a seizure at the time of stroke onset and the presence of either can falsely reassure providers that a child with new focal deficits has a complicated migraine or postictal Todd paralysis. [5, Rank 3]

Treatment

Thrombolysis with intravenous tissue plasminogen activator (IV-tPA) within a 3 to 4.5-hours window following onset of symptoms for acute ischemic stroke reduces long-term disability, however, the benefits are time dependent with the chances of a favorable outcome falling twofold for every 90-minute delay in treatment. Despite two decades of multi-pronged approach to improve tPA administration including the Joint Commission on Accreditation of Healthcare Organizations (JCACHO) accrediting “Primary Stroke Centers”, nationwide quality improvement measures such as the Get With the Guideline-Stroke (GWTG) registry reveal that only about 5% of stroke patients received tPA, and most are treated beyond 2 hours from symptom onset when tPA is less effective. With recent overwhelming evidence supporting the use of intra-arterial (IA) thrombectomy in addition to IV thrombolysis for large-vessel occlusive stroke, leaders in acute stroke care are revamping efforts to minimize time to treatment including prehospital therapeutics, patient selection for late reperfusion

therapy using efficient neuroimaging, with prehospital neuroprotection, collateral and thrombolysis enhancement to support threatened tissue until reperfusion takes place.

A main reason for treatment delay may be lack of public recognition of stroke symptoms to seek care, yet we consider other potential factors in this article. Other important factors within the control of physicians and other health care personnel include in-hospital delays (time to imaging, obtaining consent, time to laboratory studies), and improved access to stroke expertise at smaller community hospitals. [6, Rank 5]

Conventional Models

Only 15–60% of patients with stroke arrive at the hospital within 3-hours after the onset of symptoms and even less within 2-hours when IV thrombolysis is most effective. Despite significant quality improvement efforts to streamline in-hospital acute stroke care in the conventional model, there remain inherent layers of treatment delays (door-to-needle time, DTN) such as time to assessment, time to neuroimaging and laboratory studies, and time for consent, which could all be eliminated with prehospital diagnostics and therapeutics administered in a mobile stroke unit. [7, rank 3]

Apart from administering prehospital thrombolysis and neuroprotectives, early diagnosis also enables disease-specific management in the field, and early triage with targeted ambulance routing to hospitals with specialized care such as routing patients with large-occlusive strokes to comprehensive stroke centers with endovascular intervention capability, or patients with intracranial hemorrhage to hospitals with neurosurgery capability, which may in turn save valuable time for additional hospital transfers. For instance, in cases of intracerebral hemorrhage from oral anticoagulants, rapid reversal of anticoagulation (international normalized ratio [INR] < 1.4) and blood pressure lowering (systolic blood pressure [SBP] < 160 mmHg within 4 hours of symptom onset have been shown to attenuate hematoma expansion (hematoma expansion in the intervention vs control groups 18.1% vs 44.1%, odds ratio [OR] 0.25, 95% confidence interval [CI] 0.19–0.42 and lower in-hospital mortality (13.5% vs 20.7%, OR 0.60, 95%CI 0.37–0.95). Given the limited therapeutic window for effective interventions, rapid transfusion of blood products or rapid administration of nicardipine drip could theoretically be all started in the ambulance.

Emergency Medical Service (EMS) personnel training in stroke triage is imperative in both conventional and prehospital models. Several prehospital stroke scales exist, each with unique qualities, sensitivity and specificities. In the USA, the Los Angeles prehospital stroke scale (LAPSS) and the Cincinnati prehospital stroke scale are most commonly used. In Europe the Face Arm Speech Time (F.A.S.T.) scale is most widely used. LAPSS contains four history items and a blood glucose measurement with the sensitivity of 91% and specificity of 97% but it is time-consuming. Subsequently, Los Angeles Motor Scale (LAMS) is adopted from the original LAPPS score (range from 0 to 10, higher scores indicating more severe motor weakness) is simple and fast to administer. The Cincinnati prehospital stroke scale

evaluates the presence or absence of facial palsy, asymmetric arm weakness, and speech disturbance (by having the patient repeat a sentence) with sensitivity of 90% and specificity of 66% in diagnosis of stroke. F.A.S.T. scale includes three key elements from the Cincinnati scale (facial weakness, arm weakness, and speech disturbance) has a sensitivity of 79% and a positive predictive value of 78%. Regardless of the scale, the instrument needs to be easy to use by the EMS personnel to enable rapid and accurate stroke triage. [8, Rank 3]

Stroke Pathophysiology

The lack of blood flow during a stroke results in an intricate path-ophysiological response resulting in neural injury. Multiple mechanisms, including excitotoxicity, mitochondrial response, free radical release, protein misfolding, and inflammatory changes, lead to neural cell loss, but many of these pathways ultimately pave the way for recovery. Injury and death of astrocytes, as well as white matter injury, also contribute to cerebral damage. The delicate balance between detrimental or beneficial effect often relies on the timing and the magnitude of the factors involved. The inflammatory response is a prime example of a system that both propagates ischemic injury and helps promote recovery. Inflammation initially contributes to cellular injury through the release of cytokines and harmful radicals but eventually helps to remove damaged tissue, enabling synaptic remodeling. Glial cells also serve dual roles, helping to regulate the blood-brain barrier, promoting angiogenesis and synaptogenesis, but conversely forming the glial scar that may prevent further plasticity. Many of these therapies are aimed at up-regulating pathways that enhance recovery while reducing the deleterious pathways triggered by the initial ischemic insult. Further understanding and optimizing this delicate balance may facilitate development of effective stroke therapeutics. [9, Rank 3]

<u>Excitotoxicity</u>

CNS ischemia results in a deficiency of glucose and oxygen leading to the inability of neuronal cells to maintain normal ionic gradients. Depolarization of these neurons leads to excessive glutamate release resulting in the intracellular influx of calcium, triggering cell death pathways such as apoptosis, autophagocytosis, and necrotic pathways. This process has been termed excitotoxicity and is mediated largely through the glutamatergic pathways involving N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs), and kainate receptors. The role of calcium in excitoxicity also remains complex and has numerous effects in the ischemic environment. The intracellular increase in calcium triggers mitochondrial dysfunction and activation of free radicals, phospholipases, and proteases, which lead to cell death or injury. Interestingly, the interplay between the cells is also critical to the spread of injury after ischemic insults. Blockage of the gap junctions between cells in the adult brain reduces neuronal death, potentially indicating the important interactions that occur between cells during neuronal damage. These processes also promote cerebral edema, which has clinical import in the first few days after a stroke. Numerous therapeutic approaches have centered on interrupting

pathways triggered by excitotoxicity to improve stroke recovery, and while often successful in animal models, translation of these findings into the clinic remains challenging. [10, Rank 5]

Mitochondrial Alterations

The mitochondria play a critical role in cell energy homeostasis and are thus prominently involved during ischemia when the energy balance is disrupted and ATP synthesis is altered. The rapid influx of calcium experienced with excitoxicity leads to excess accumulation in the mitochondria, causing dysfunction, which leads to mitochondrial permeability transition pore (mtPTP) opening and cytochrome c release. These events create mitochondrial swelling and membrane collapse, initiating cell death cascades such as apoptosis. The reactive oxygen species (ROS) created by the mitochondria also play a prominent role in reperfusion injury and cell death in the ischemic environment. Maintaining mitochondrial integrity and limiting their induction of apoptotic and oxidative stress pathways in the cell are important avenues to preventing widespread cell toxicity from an ischemic insult. [11, rank 3]

Free Radicals

Brain ischemia also triggers free radicals, which contribute to the oxidative stresses on neural tissue. The influx of calcium triggers nitric oxide (NO) production by nitric oxide synthase (NOS) that leads to injury through the formation of oxygen free radicals and the production of peroxynitrite (ONOO–). The mitochondria undergo dysfunction during ischemia, leading to further oxidative stress. NADPH oxidase also plays a critical role in ROS production in the setting of excitotoxicty and ischemia. Furthermore, chimeric bone marrow studies have shown that inflammation contributes with neutrophils releasing inducible NOS (iNOS), which leads to toxic levels of NO. Free radicals trigger the PI3-kinase/Akt pathway as well as upregulate the transcription factor NF-κB. Interestingly, the timing and environment of activation of this pathway likely determine whether stroke recovery is improved or impeded by this signaling cascade. Other pathways of interest are the transient receptor potential (TRP) channels. TRP channels, TRPM7 specifically, are linked to free radicals in ischemia and likely contribute to increasing the influx of calcium and cellular toxicity experienced during decreased oxygenation. Not only do free radicals contribute to initial toxicity, they also prevent recovery, which makes them an important post-stroke therapeutic target. Numerous methods have reduced the oxidative stress from free radicals in ischemic injury and shown neurologic improvement in preclinical models. Combining the regulation of these pathways with other ischemic injury mechanisms may lead to novel therapeutics. [12, Rank 5]

Protein Misfolding

The largest stores of intracellular calcium reside in the endoplasmic reticulum (ER), an organelle that regulates protein synthesis and responds to protein misfolding. These

processes are largely affected by ER stress induced by ischemic injury. As excitotoxic changes occur in neural cells, the sarcoplasmic/ER calcium ATPase (SERCA) pump fails due to energy depletion and adds to the occurrence of cell death. The increased accumulation of misfolded proteins also trigger the protein kinase-like ER kinase (PERK) pathway regulating eIF2α kinase activation, which halts new protein synthesis. The phosphorylation of eIF2α has been explored as a means to alter damage in cerebral ischemia. Inositol requiring enzyme 1 (IRE1) is another protein involved in the misfolding of proteins that has been shown to induce apoptotic pathways during periods of ER stress. Chaperones (such as oxygen-regulated protein 150 kDa and binding immunoglobulin protein), which normally guide protein synthesis, are also altered in ischemia, and upregulation of these chaperones may reduce apoptosis and limit damage from ischemia. The cumulative effect of SERCA pump failure and chaperone misfunctioning make ER stress and its role in protein misfolding, the important targets for acute stroke therapies. [13, rank 3]

Astrocytic Changes and White Matter Injury

The glial cells (astrocytes and oligodendrocytes) surrounding neurons and their connections play an integral role in the brain's response to ischemia and recovery. Axons and glial cells are intimately interwoven, forming the connections and signals that compose neural activity and are poised as key therapeutic targets to enhance recovery mechanisms and reduce injurious ones. At baseline, white matter receives less blood supply than gray matter, and this may predispose white matter to ischemic damage with milder variations in blood flow. During ischemic injury, glial cells are damaged by similar injury pathways to neurons including glutamate toxicity. Ischemia also triggers P2X7 receptors on oligodendrocytes, which contribute to calcium overload and mitochondrial depolarization. One of the key differences between the effects of ischemia on white matter compared with gray matter is the reliance on oligodendrocytes for functional deficits as well as the reduced influence of NMDA-type glutamate receptors on white matter injury.

After the acute response to hypoxic conditions, the glia also help to modulate inflammation and recovery. Although the glial scar has been shown to prevent new growth, it also exhibits positive effects of helping to restore the integrity of the blood-brain barrier. Additionally, reactive astrocytes, associated with formation of the glial scar, also modulate trophic factors, which enhance recovery. Thus, glia play a prominent role in modulating the injury cascade and eventual recovery after stroke. [14, rank 3]

Inflammatory Response and the Role of Blood-Brain Barrier

The immune system plays a vital role in the CNS's response to ischemia and to eventual recovery of function. An intricate cascade of immune cells and inflammatory factors cause blood-brain barrier breakdown, remodeling of the post-stroke tissue, and also offer a margin of neuroprotection from the harsh excitotoxic post-stroke environment of increased free radicals and enzymes. Initially, microglia respond to the ischemic insult followed by an

increase of dendritic cells, macrophages, and lymphocytes, and as astroglia are reduced and blood-brain barrier breakdown occurs, an influx of neutrophilic cells permeates the infarct and peri-infarct region. Proinflammatory cytokines (i.e., tumor necrosis factor-α and interleukin-1β) are also released as well as free radicals by the immune cells in the post-stroke tissue, which increase the inflammatory response and upregulate cell adhesion molecule expression, further propagating the immune response. Immune cells also release inducible NO synthetase, which contributes to the detrimental effect of NO in brain ischemia. Additionally, matrix metalloproteins (MMPs) and myeloperoxidase (MPO) production are elevated by the immune response, both of which are major factors leading to blood-brain barrier breakdown. Inhibiting the acute inflammatory response after stroke has been shown to decrease injury and improve neurologic outcome in rodent stroke models, but has not yet been translated into the clinic. [15, Rank 2]

Components of the complement cascade play a role in ischemic injury and recovery. The amount of complement proteins increases after ischemia. Evidence suggests that complement proteins tag synapses for removal by microglia to enable synaptic pruning and remodeling. Another role of complement proteins (C3a and C5a, in particular) is protecting neurons from the NMDA excitotoxicity that occurs post-stroke. Immune cells such as eosinophils also produce trophic factors such as nerve growth factor (NGF) and neurotrophin-3 that promote neuronal outgrowth and may have a significant impact on post-infarct plasticity. Microglia also play a prominent role producing glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which promote neural growth and healing. Insulin-like growth factor (IGF-1), another molecule modulated by microglia, enhances axonal growth as well as neurogenesis in the subventricular zone (SVZ) to improve stroke recovery. Cytokines, such as transforming growth factor-β and interleukin-10, often serve dual roles of driving the inflammatory response but also promoting tissue repair and resolution of inflammation depending on timing and the environment.

The multifaceted immune response has both a beneficial and deleterious effect on the surviving tissue. The timing and levels of inflammatory factors and cells contribute to the balance of post-stroke injury and the restorative process. The immune response has a positive role on recovery by pruning unwanted synapses and allowing for the formation of new growth and connections. However, there is also a negative effect of the inflammatory response with rodent models showing decreased stroke volume and infarct size in immunodeficient animals. While neutrophils release cytokines and radicals that worsen the inflammatory response, inflammatory cells also help remove debris and damaged tissue to facilitate recovery. The balance of the inflammatory response after stroke is critical for recovery, and investigation into the components that lead to improved recovery and plasticity versus those that worsen ischemic damage is an exciting area for further research and translational investigations. [16, Rank 5]

Various Stroke Therapies

The complex injury pathways described above often disrupt the cortical maps that form the neural representation of our body. Increased spine formation and axonal sprouting weeks after ischemia demonstrate enhanced neural plasticity in the peri-infarct area and contralesional hemisphere as brain regions reorganize, likely to restore function. Alterations in synaptic function and vasculature have been shown to correlate with behavioral improvement after stroke as the brain remaps to compensate for damaged networks. Because of the complexity of the restorative processes that occur after the initial ischemic damage, a single mechanistic pathway will likely not be sufficient to greatly improve functional outcomes. Strategies such as cell therapies, stimulation, or mild hypothermia that affect several of these pathways, or a combination of therapeutic approaches, may prove to be the most promising for clinical translation.

Currently, the mainstay of acute stroke therapy is intravenous administration of tissue plasminogen activator (tPA), which has been FDA approved within a narrow time window. Endovascular therapies utilizing intra-arterial mechanical or chemical thrombolysis also improve outcomes. After the acute time period, focused physical rehabilitation of the injured area is the primary current therapy that is proven to be effective. Re-organization of the cortex has been observed with rehabilitation in pre-clinical models as well as in humans. While rehabilitation can be effective, and encouraging results have been demonstrated with constraint induced movement therapy and other techniques, the extent of neurologic recovery is still limited and novel approaches to augment or enhance the body's endogenous regenerative abilities are required. [17, Rank 5]

Restoring Circulation

Clinical treatments in use currently focus on restoration of blood flow to the penumbral tissue. Dendrites and their spine morphology are adversely affected by ischemia; however, recovery is possible even with severe ischemia if blood flow is restored quickly. After many decades of pessimism surrounding stroke therapies, tPA given intravenously showed efficacy in a major clinical trial if given within 3 hr of symptom onset. More recently, intravenous tPA was shown to be advantageous up to 4.5 hr after stroke in a large European trial. Endovascular interventions of mechanical and chemical clot removal are often used clinically and have shown great promise with recent clinical trials demonstrating benefit within the acute timeframe. The use of noninvasive transcranial Doppler ultrasound-assisted thrombolysis (in combination with intravenous tPA) is also being tested in early phase clinical trials . Given the variety of strokes and patient differences in collaterals and vasculature, selecting the correct patients may be critical for the ultimate success of these therapies. Unfortunately, a vast majority of stroke patients are not able to receive the acute treatments because of the narrow time windows. Further investigations studying the inflammatory and oxidative stresses as blood flow is restored will also help elucidate how the brain heals from ischemic injury. Therapies targeting later time windows are also needed to help recover from tissue that has been damaged before blood flow can be restored. [18, Rank 5]

Disruption of Injury Pathways and Neuroprotection

The peri-infarct region appears to contain the highest potential for plasticity after stroke, with factors promoting growth and axonal sprouting expressed in this territory. Minimizing the damage to these areas and maximizing the potential for restoration are the goals of many of the neuro-protective strategies. Mechanisms that degrade and remodel the extracellular matrix (ECM), such as matrix metalloproteinases, are also upregulated in this region. Additionally, angiogenesis and neurotrophic factors such as BDNF, which likely promote plasticity after stroke, are modulated in the area surrounding the infarct. Despite their success in animal models, clinical trials for multiple neuroprotective strategies have proven uninspiring. Multiple explanations exist for this. One reason is the inadequacy of current animal models. The human brain and response to injury is far more complex than in the rodent. The variability in human anatomy is also difficult to represent in mouse models genetically engineered to be identical. Additionally, young rodents are most commonly used in the laboratory setting due to expenses, although differences in response to stroke are seen between young and older animals. Another difference is that outcome measures can be much more precisely designed and evaluated in the preclinical setting compared with clinical scales that may not truly assess the subtleties of stroke phenotypes. Timing of these therapies is another critical component and is much more controlled in the lab environment compared with clinical application, where administration of a drug can be delayed for hours or days depending on the patient's presentation. [19, Rank 5]

While affecting a single pathway in an animal model is sufficient to prevent injury, multiple pathways may need to be disrupted in humans to yield similar results. Mild brain hypothermia (33°C), which has become the gold standard for acute neuroprotection in rodent stroke models, improves neurologic outcomes for patients with a particular type of stroke (global cerebral ischemia) secondary to cardiac arrest and neonatal hypoxic-ischemic encephalopathy. Therapeutic hypothermia after cardiac arrest has now become a recommended guideline for clinical care. Mild hypothermia is currently being investigated as an acute stroke therapy, with trials to date proving the feasibility of this approach. Another promising acute neuroprotective strategy targets the post-synaptic density-95 protein (PSD-95). PSD-95 connects NMDA receptors to signaling pathways necessary for the excitotoxic cascade and inhibiting these circuits reduces stroke volume in primates. A recently published prospective, randomized, double-blind controlled trial demonstrated safety and improved neurologic outcome and fewer acute infarcts in patients undergoing endovascular intracranial aneurysm repair who received a PSD-95 inhibitor. As barriers to accurately mimic clinical practice in the laboratory are reduced and the ability to manipulate multiple recovery pathways are improved, more effective neuroprotective therapies can be developed. [20, Rank 3]

Clues for Specific Etiologies

Certain historical features, symptoms, and signs may serve as clues toward specific stroke etiologies. Recent minor trauma or sudden neck movements, including chiropractic neck manipulation or vigorous exercise, are associated with arterial dissection. Patients with cervical artery dissection will frequently complain of headache or neck pain. A painful Horner syndrome, or coexisting cranial neuropathies, should always raise suspicious for dissection; all cranial nerves except the olfactory nerve may be affected by dissection.

Clinical clues to the presence of an underlying arteriopathy include headache (particularly recurrent thunderclap headache), recurring stereotyped TIAs, psychiatric disturbances, skin rash, exposure to vasoconstrictive agents, pregnancy, hormonal contraceptive use, head trauma, and HIV infection. Transient cerebral arteriopathy is the most common cause of stroke in children, but typically has no clinical clues. Genetic disorders are suggested by abnormal eye and skin examination findings such as retinal arteriolar irregularities, ectopia lentis (Marfan syndrome), iris hamartomas and optic nerve tumors (neurofibromatosis), cataracts, corneal opacities, angiokeratomas (Fabry disease), hyperelastic skin (Ehlers-Danlos type IV), and neurofibromas or café-au-lait spots (neurofibromatosis). On brain imaging, it is important to consider stroke lesion topography; e.g., a unilateral “string-of-pearls” appearance may indicate middle- or internal-cerebral artery stenosis.

A history of recent prolonged immobility, such as after recent surgery, should raise suspicion for paradoxical embolism through a patent foramen ovale (PFO). Fevers, back pain, and joint pain should raise concern for endocarditis. Clues for a hypercoagulable state include a history of deep venous thrombosis or multiple miscarriages. Skin examination may reveal underlying coagulation problems, vasculitis, endocarditis, or stigmata of IV drug abuse. [21, Rank 3]

Laboratory Tests

Given the broad spectrum of etiologies, the fear of litigation from missing ominous or rare causes, and the absence of evidence-based diagnostic algorithms, young stroke patients are invariably subjected to a wide array of diagnostic tests, often ordered simultaneously at the time of presentation. This includes the usual test panel performed for any stroke patient, and specialized tests for causes relatively more frequent in young patients. The clinical clues outlined above should be considered to tailor the diagnostic work-up, and an organized, stepwise evaluation should follow. [22, Rank 5]

The yield of several diagnostic tests was investigated in a small retrospective study. The yield was relatively low for Holter monitoring (1%) and toxicology screening (5%), and relatively high for cardiac ultrasound (51%) and cerebral angiography (64%). Others have shown a similar high yield for cerebral angiography. Because younger patients are at higher risk of developing leukemia and brain tumors from CT scans, exposure to radiation should be limited when possible. The clinical significance and treatment implications of findings such as a positive hypercoagulable panel test result, or a PFO on cardiac ultrasound, remain controversial. Nevertheless, in view of the variable yield and high cost of specialized tests, it

seems justified to routinely perform high-yield tests such as cardiac ultrasound and vascular imaging in young stroke patients. More research is warranted to determine the cost-effectiveness of diagnostic tests and design appropriate strategies to evaluate stroke in the young. [23, Rank 3]

Emergent treatment of younger stroke patients is similar to older patients. Recommendations for physiologic management, e.g., blood pressure, temperature, glucose, and oxygenation, as well as thrombolysis, are the same as for older stroke patients. Younger patients benefit from access to stroke expertise and ideally should be admitted to comprehensive stroke centers with neurocritical care units. Those with large strokes, especially malignant middle-cerebral artery infarction, require aggressive neurocritical care monitoring, intracranial pressure management, and early assessment for decompressive hemicraniectomy, which not only lowers mortality but also improves long-term neurologic and functional outcomes. Several studies have shown that reperfusion strategies are efficacious and appear to be safe in young adults. For example, in one study, young patients (18–50 years) had significantly better functional outcome and lower rates of symptomatic brain hemorrhage and 3-month mortality compared with older patients (51–80 years). At present, thrombolysis is approved only for those aged 18 years and older; the ongoing NIH-funded Thrombolysis in Pediatric Stroke trial will provide safety and dosing data for thrombolysis in children and adolescents. [24, Rank 4]

Prognosis

Prognosis is an important issue in premature stroke because of the longer expected survival compared with older people with stroke. In addition, those affected by stroke in young adulthood often have significant stress, and primary responsibility for generating income for the family or providing child care. Prognosis will be discussed in relationship to mortality, stroke recurrence, and other vascular events, poststroke epilepsy, functional outcome, poststroke depression and quality of life, return to work, and other social consequences.

Mortality rates in a large study of first IS in patients aged 15 to 49 years were 2.7% (95% confidence interval [CI] 1.5%–3.9%) at 1 month, 4.7% (95% CI 3.1%–6.3%) at 1 year, and 10.7% (95% CI 9.9%–11.5%) at 5 years, consistent with prior smaller studies. Five-year mortality was higher for those aged 45 and older (14.7%) vs those younger than 45 (7%), and higher for large-artery atherosclerosis (approximately 30%) and cardioembolism (approximately 20%) vs other determined or undetermined etiology or small-vessel disease (approximately 5%–7%). The 5-year rate for stroke recurrence and other vascular events, both nonfatal and fatal, was 11.5% (95% CI 9.2%–13.7%); independent predictors of higher rates were type-1 diabetes, heart failure, large-artery atherosclerosis, prior TIA, and increasing age. The 5-year rate for poststroke epilepsy among patients with first IS ages 15 to 49 was 10.5% overall, but 34% among patients with severe neurologic deficits from index stroke. [25, Rank 5]

Functional independence (no or slight disability and able to look after own affairs without assistance; modified Rankin Scale score ≤2) ranged from 78% to 85% to 94%. Diabetes and severe neurologic deficits at admission were predictors of poor functional outcome. Although most patients regained functional independence, there was a high rate of poststroke depression ranging from 28% to 46%; fatigue, reported in 54%; and impaired quality of life, particularly in the SF-36 dimensions of physical functioning, role limitations due to physical health, and social functioning. Estimates of the percent returning to work after stroke vary, but have been reported at 42% to 53% with 23% of those returning to work requiring adjustments in their occupation. Other social consequences of stroke have not been well studied in large representative samples of young stroke patients. Young adults with stroke frequently are parents of young children. While quantitative estimates are lacking, this role may be impaired in some stroke patients. Limited data are available on changes in family structure; a French study reported a 7% divorce rate after a mean follow-up of 3 years. [26, Rank 3]

Mobile Stroke Unit

Time is of the essence in both acute coronary syndrome (ACS) and cerebral infarct. Endovascular reperfusion therapies for acute myocardial infarction (AMI) and ischemic stroke evolved in parallel: Beginning for intravenous fibrinolysis, followed by intra-arterial fibrinolysis, then progressing to mechanical thrombectomy. The concept of tissue-time in heart attack and brain attack prompted both Cardiology and Vascular Neurology to initiate prehospital therapy in the ambulance to maximize outcome. [27, Rank 3]

<u>Prehospital electrocardiogram (EKG) analogy</u>

Prehospital triage and identification of patients with ACS are critical since each minute of delay from symptom onset to intervention for increases mortality. Studies have shown that abnormal prehospital EKG signs of ischemia (ST elevation, ST depression, T-wave inversion) drive early treatment decisions for patients with myocardial infarction such as the decision to route the ambulance to what may be the closest hospital for a further one that offers definitive cardiac treatment. Moreover, EKG signs of ischemia are independent predictors of adverse hospital outcomes, a final diagnosis of ACS, and direct admission to acute coronary care units. With these evidences, conducting a prehospital EKG while in the ambulance is becoming the standard of care and the American Heart Association designated prehospital EKG as a class I recommendation in its 2010 Cardiac Life Support guidelines. [28, Rank 5]

<u>Stroke Emergency Mobile (STEMO)</u>

Analogous to prehospital EKG that enables earlier diagnosis for AMI, noncontrast head CT enables earlier ischemic vs hemorrhagic stroke diagnosis. Amobile stroke unit is equipped with CT scanner, point-of- care laboratory, telestroke connectivity, thrombolysis capability, CT technician, EMT with or without a stroke. Deployment of the mobile stroke unit might

potently reduce time to treatment by allowing prehospital identification of patients with probable large artery occlusion, facilitating their in-hospital treatment by prehospital notification, earlier assembly of the endovascular team and angiography suite preparation, and shorter in-house delays incurred by acquiring imaging and laboratory data and treating with tPA, perhaps allowing bypass of ED evaluation altogether. [29, Rank 4]

Over a 21-month period, the STEMO was dispatched every other week 1804 times, and 177 patients were treated with tPA in the ambulance prior to transport to the ED. The intervention resulted in a 25-minute reduction in time from alarm to tPA treatment compared with non-STEMO weeks (95%CI, 20 to 29-minute; $P < 0.001$), with 58% of patients treated within 90minutes of symptom onset (vs 37% in control), low rates of symptomatic intracerebral hemorrhage (2.2%), and notably no instances of CT malfunction. No differences were seen in discharge status, but the study was not powered or designed to assess clinical outcomes other than safety. PHANTOM-S affirmed that prehospital delivery of tPA significant shortens the time of tPA administration from symptom onset, culminating a 20-year concerted effort for prompt and prevalent administration of tPA.

In a post-hoc analysis of PHANTOM-S, researchers aimed to evaluate whether prehospital management in the STEMO improves the triage of patients with stroke. They found that 11.6% of patients with cerebrovascular events were sent to hospitals without Stroke Unit in conventional care when compared with 5.5% patients in STEMO care (P<0.01). In patients with ischemic stroke, STEMO care reduced transport to hospitals without Stroke Unit from 10.1% to 3.9% (P<0.01). The delivery rate of patients with intracranial hemorrhage to hospitals without neurosurgery department was 43.0% in conventional care and 11.3% in STEMO care (P<0.01). There was a slight trend toward higher rates of patients discharged home in neurological patients when cared by STEMO (63.5% versus 60.8%; P=0.096). The study provided clear evidence that prehospital triage of patients with cerebrovascular events improved ambulance routing to specialized hospitals.

Future studies are needed to exam the short-term and long-term clinical outcomes of a mobile stroke unit. Houston developed the first mobile stroke unit in the United States. Future studies are also needed to test feasibility and utility of prehospital administration of neuroprotective to stabilized penumbra and thrombolytic enhancers to optimize durable recanalization. [30, Rank 3]

Neuroprotectives

Developing ways to improve reperfusion therapy for acute ischemic stroke has long been an active area of research in the past 3 decades with countless failures, and also more encouragingly, recent successes. Neuroprotective therapies for patients with acute ischemic stroke are treatments that enable brain cells to endure injury from reduced blood flow. Neuroprotective agents block the molecular, cellular injury in hypoxic–ischemic tissues. Often safe in hemorrhagic (except thromoblytics) as well as ischemic stroke, many neuroprotective agents can be given prior to brain imaging, including in the prehospital

setting. By stabilizing threatened brain tissue, early neuroprotective therapy may increase the volume of salvageable tissue that is still present at the time that reperfusion therapy can be started, after hospital arrival and initial brain imaging.

Categories of neuroprotective agents have grown to include the following: suppressors of neuronal metabolism, calcium entry blockers, excitotoxic neurotransmission blockers, free radical scavengers, nitric oxide–related interventions, apoptosis inhibitors, hyperpolarization agents that inhibit peri-infarct depolarization, promoters of membrane repair, anti-inflammatory and anti-cytokine agents, and neurotrophic agents. More than 70 neuroprotective agents have been tested in more than 140 randomized, controlled, clinical trials in acute ischemic stroke, enrolling over 25,000 patients, but no agent was unequivocally beneficial in definitive phase III trials. A key reason for failures was marked delay in delivery of neuroprotective agents in previous clinical trials. Preclinical trials in rodent and nonhuman primate experimental suggest the duration of the therapeutic window within which neuroprotective intervention can ameliorate bioenergetic failure in the ischemic shadow is very brief, generally less than 2–3hours. Most animal studies of neuroprotective agents initiate therapy within 1–60 minutes after ischemia onset. Unfortunately, overwhelming majority of neuroprotective trials had time to randomization up to 48-hours, well after the critical period for stabilizing the penumbral region had ended. An analysis of 5345 patients enrolled in six neuroprotective trials performed in the 1990s and 2000s showed that only 0.2% of patients received the study agent in the first hour after symptom onset and only 1.2% in the second hour; 6.3% received the agent in the third hour; and 92.3% were treated beyond 3 hours. [28, Rank 3]

Prehospital therapy has been proven beneficial for other acute neurologic conditions. In status epilepticus, the Prehospital Treatment of Status Epilepticus trial showed that paramedic initiation of anticonvulsants in the field is safe, reliable, and yields better clinical outcomes than standard in-hospital therapy. In cardiac arrest and global cerebral ischemia, the Melbourne hypothermia trial showed benefit of neuroprotective temperature reduction initiated in ambulances before hospital arrival. Finally 2015 in stroke, The Field Administration of Stroke Therapy– Magnesium (FAST-MAG), a pivotal phase 3 trial was published affirming the feasibility of administering prehospital acute stroke treatment within 2 hours after the onset of symptom during when neuroprotective agents and thrombolytic agents exert most effects on stroke outcomes. In the following section, we'll describe intervention clinical trials of several prehospital stroke therapeutics, including neuroprotectives (magnesium sulfate, NA-1), antihypertensives (glyceryl trinitrate, lisinopril), collateral enhancement (volume expansion), thrombolysis enhancements (glycoprotein IIb/IIIa eptifibatide, thrombin inhibitor argatroban, and transcranial Doppler ultrasonography with or without microbubbles). [25, rank 2]

<u>Magnesium</u>

Magnesium exerts both vasodilatory and direct neuroprotective and glioprotective effects in cerebrovascular disease by impeding calcium influx into ischemic neurons and prevents cell death. It is also inexpensive and widely available clinically. Numerous preclinical models of stroke had shown benefit. FAST-MAG is a randomized, placebo-controlled trial enrolled 1700 patients presented with acute ischemic stroke with a mean pretreatment score on the Los Angeles Motor Scale of stroke severity of 3.7±1.3 (range, 0 to 10, with higher scores indicating greater motor deficits). Ischemic stroke was found in 73.3% of patients, intracranial hemorrhage in 22.8%, and a stroke-mimicking condition in 3.9%. The median time to treatment from symptom onset was 45 minutes (interquartile range [IQR] 35–62), and 74.3% of patients received the study-drug infusion within the first hour after symptom onset. There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale (mRS) between patients in the magnesium group and those in the placebo group (P = 0.28); mean scores at 90 days did not differ between the magnesium group and the placebo group (2.7 in each group, P = 1.00). No significant between-group differences were noted with respect to mortality (15.4% in the magnesium group and 15.5% in the placebo group, P = 0.95) or all serious adverse events. While FAST-MAG did not show benefit in improving 90-days disability, it was a pivotal trial proving that it is possible to conduct prehospital clinical studies in ambulance, open the door for future prehospital study within the 'golden hour' when neuroprotectives and thrombolysis are most effective in stroke care. [24, Rank 4]

NA-1

NA-1 is another promising neuroprotective agent. It is a cell-permeant eicosapeptide that perturbs the protein–protein interactions of PSD-95, a postsynaptic scaffolding protein. PSD-95 links NMDA glutamate receptors to neurotoxic signaling pathways, and NA-1 disrupts these links and inhibits stroke damage. Preclinical studies have shown that NA-1 reduces the volume of strokes after middle cerebral artery occlusion and reduces the volume and number of strokes after the intra-arterial injection of small emboli. Evaluating Neuroprotection in Aneurysm Coiling Therapy (ENACT) is a double-blind, randomized-controlled study to assess whether NA-1 would reduce the volume and number of periprocedural ischemic stroke in those with ruptured or unruptured intracranial aneurysm. Authors found that patients in the NA-1 group sustained fewer ischemic infarcts than did patients in the placebo group, as gauged by diffusion-weighted MRI (adjusted incidence rate ratio 0.53, 95%CI 0.38–0.74) and fluid-attenuated inversion recovery MRI (0.59, 0.42–0.83). As for ischemic stroke, Field Randomization of NA-1 Therapy in Early Responders (FRONTIER) is an ongoing trial to assess if NA-1 may have neuroprotective effects on stroke functional outcome. [25, Rank 3]

Antihypertensives

Antihypertensives may have a role in both ischemic and hemorrhagic stroke. In ischemic stroke, elevated blood pressure above 185/110 mmHg remains a common reason for

withholding IV tPA, early initiation of antihypertensive therapy to reach this goal SBP in order to administer tPA is supported by positive results in multiple clinical trials. In intracranial hemorrhage, studies using CT imaging report hematoma growth in greater than 70% of patients within the first three hours of symptom onset with only 11–12% expanding after the first three hours. Treatment outside of this phase is unlikely to yield significant effect on outcome, and the earliest time windows for treatment, including pre-hospital treatment of blood pressure may be needed to prevent clinical deterioration and obtain optimum clinical results. Clinically, as many as three in ten patients who are initially alert during paramedic evaluation within the first two hours of onset will have significantly deteriorated before arrival to the hospital.

Glyceryl trinitrate (GTN) has also demonstrated neuroprotective and antihypertensive properties in preclinical stroke models. GTN acts as an inhibitor of apoptosis through formation of nitric oxide equivalent molecule that nitrosylates the redox modulatory site at the NMDA receptor. This has the neuroprotective effect of inhibiting NMDA receptor-mediated neurotoxicity. In cerebral ischemia reperfusion models, administration of NO donor was shown to decrease free radical levels and reduce brain infarct volume. Additionally, transcranial Doppler and xenon CT studies of cerebral blood flow have shown that transdermal GTN increases or maintains cerebral perfusion in acute ischemic stroke patients despite decreases in mean arterial pressure. [18, Rank 5]

Efficacy of Nitric Oxide in Stroke (ENOS) is a large multicenter, randomized, placebo-controlled trial enrolling about 2000 patients in each arm presented with acute stroke symptoms within 3 hours, systolic blood pressure of 140–220mmHg, could be treated with 7 days of transdermal glyceryl trinitrate (5mg daily) or placebo within 48 hours of symptom onset. There was no difference in 90-days mRS (odds ratio 1.01, 95%CI 0.91–1.13, P=0.83) between the groups. However, subgroup analysis showed favorable 90-days outcomes among those receiving glyceryl trinitrate within 6-hours after symptom onset (P=0.031) suggesting that transdermal GTN may have a role in prehospital stroke treatment.

Indeed, in Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT) is a small randomized-controlled trial involving 80 patients (25 GTN, 16 no GTN) done in the ambulance within less than 4 hours of stroke onset. Systolic blood pressure at 2 hours was 153±31mmHg vs 174±27mmHg (P=0.04), in GTN vs no GTN groups, respectively. The mean 90-days mRS was 3 vs 5 (P=0.17), 90-days mortality was 15% vs 38% (P=0.15), and adverse events: 56% vs 63% (P=0.75). The trial demonstrated that paramedics can successfully enroll patients with ultra-acute stroke into an ambulance-based trial and that GTN reduces systolic blood pressure at 2 hours and seems to be safe in ultra-acute stroke. Similarly, Paramedic Initiated Lisinopril For Acute Stroke (PIL FAST) is another double-blind RCT testing the effect of prehospital administration of Lisinopril vs placebo on BP treatment. Median time from stroke onset to treatment was 70minutes. The study again demonstrated feasibility of prehospital hyperacute stroke treatment. [22, Rank 3]

Treatment for Thrombolysis Enhancement

Combined therapeutics is another promising prehospital therapeutic that could be co-administered in the mobile stroke unite to improve sustained recanalization and stroke outcome. IV thrombolysis alone opens about 50% of occluded arteries, paradoxically, lysis of an occluding clot has prothrombotic effect such that 14–34% of these re-occlude within 2 hours leading to worse outcomes. Rupture of plaque releases a pool of trapped thrombin and exposes tissue factor, surface-bound von Willebrand factor and collagen, which activate the intrinsic and extrinsic coagulation cascades. Optimal reperfusion treatment may require several components including antiplatelet and antithrombin agents, in addition to fibrinolytic drug, in order to prevent re-thrombosis. In stroke, combination pharmacotherapy strategies to expand the intravenous fibrinolysis time window beyond 4.5 hours are currently under active investigation. A rational combination of agents with additive effects on clot lysis and clot formation may yield higher rates of arterial recanalization, lower rates of re-occlusion, reductions in the dose of fibrinolytic agent required, and reduced frequency of hemorrhage transformation. Furthermore, combining neuroprotective therapies with fibrinolytics may potentiate treatment benefit and extend the time window in which salvageable tissue persists to be rescued by reperfusion. [21, rank 4]

<u>Direct Thrombin Inhibition</u>

The thrombin inhibitor Argatroban (GlaxoSmithKline, Philadelphia, PA), directly and selectively inhibits the action of free and clot-associated thrombin. Safety has been demonstrated with and without thrombolytics or aspirin in patients with acute myocardial infarction(MI). In animal stroke models, argatroban safely augments the benefit of tPA by improving flow in the microcirculation, increasing the speed and completeness of recanalization, and preventing reocclusion. The Argatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-1) study showed that argatroban (mean doses of 1.2 and 2.7 μg/kg per minute) given within 12 hours of ischemic stroke provides safe anticoagulation without an increase in intracerebral hemorrhage (ICH). No clinical benefit was observed but it should be noted that patients did not receive tPA treatment.

The Argatroban TPA Stroke Study (ARTSS), a pilot safety study of full dose IV-tPA(0.9mg/kg)+Argatroban recently completed enrollment. Eligibility included patients aged 18 to 85 years admitted within 4.5 hours of stroke onset and meeting the criteria for intravenous-tPA therapy. Patients were also required to be within the NIH stroke scale (NIHSS) limits of 5–20 on the left hemisphere and 5–15 on the right hemisphere, have a proximal intracranial arterial occlusion measured by TCD or CT-angiogram (CTA), and an INR ≤1.5. Subjects received IV-tPA+argatroban: 100 μg/kg bolus started during the tPA infusion then followed by a 1 μg/kg infusion for 48 hours. Argatroban was titrated to a target partial thromboplastin time (PTT)=1.75 times baseline. The first 15 patients were enrolled at the 1μg/kg dosage and 2 patients experienced symptomatic ICH (sICH) (13%, 95% confidence

interval: 4–48%). However, at 2-hours, there was a non-significant trend towards greater rates of complete recanalization compared to historical, IV-tPA treated patients from the CLOTBUST study (43% vs. 13%, *P*=0.25). Before exploring the safety of higher-dose Argatroban (3µg/kg titrated to goal PTT of 2.25 times baseline), the FDA required an additional 50 patients enrolled at the 1.75 dose. [20, Rank 5]

Thrombolysis plus thrombin inhibitor (argatroban)

Argatroban in a thrombin inhibitor that directly and selectively inhibits free and clot-associated thrombin. Safety of argatroban has been demonstrated with thrombolytics or aspirin in patients with acute myocardial infarction with major bleeding risk of 2.6% and 4.6% for low-dose and high dose-argatroban, lower than the control of 10%. Unlike the soft pericardial sac that surrounds the heart, the brain is encased in hard skull of which hemorrhagic conversion is a neurologic emergency that can be life-threating. Careful evaluation of intracranial bleeding risk is necessary prior to applying combined tPA and argatroban clinically. In animal stroke models, argatroban safely augments the benefit of tPA by improving flow in the microcirculation, increasing the speed of clot lysis.

The Argatroban tPA Stroke Study (ARTSS) is a pilot safety study of full-dose IV tPA (0.9 mg/kg) enrolled 65 patients in a prospective, single arm trial of combined standard dose IV tPA plus argatroban infused for 48-hour adjusted to a target partial thromboplastin time (PTT) 1.75 times of baseline. Among the first 20 patients enrolled, symptomatic intracerebral hemorrhagic rates were low (4%). Partial or complete recanalization at 2-hour was achieved in 70% of patients. Complete recanalization at 2-hour trended higher in the combined argatroban plus tPA group than in historical controls (35% vs. 13%). The pilot study showed that combined argatroban and tPA is potentially safe in patients with moderate neurological deficits due to proximal intracranial arterial occlusions and may produce more complete recanalization than tPA alone. Phase IIb of ARTSS-2 is ongoing to further evaluate safety and efficacy along with another trial, Minimizing Onset of Stroke Treatment Time stroke trial (MOST). [20, Rank 3]

Thrombolysis plus platelet inhibitor GPIIb/IIIa (eptifibatide)

Glycoprotein (GP) IIb/IIIa antagonists potently block the platelet GP IIb/IIIa receptor, the final mediator of aggregation. GP IIb/IIIa a reduce thrombus growth and prevent re-occlusion after mechanical or lytic-driven recanalization. Moreover, GP IIb/IIIa antagonists have the ability to dissolve platelet-rich clots and to improve flow in coronary and cerebral microcirculation. In practice, GPIIb/IIIa inhibitors are commonly used in high-risk acute MI and to prevent percutaneous coronary stent occlusion. Combination GP IIb/IIIa inhibitors plus IV thrombolysis resulted in higher rates of thrombolysis in myocardial ischemia 3 reperfusion (compared with non-GPIIb/IIIa arms) in Phase II studies.

Eptifibatide is a highly selective GP IIb/IIIa antagonist tested in combination with tPA within 3 hours of onset in a multicenter phase 2 dose-escalation study involving 126 patients (CLEAR-ER) randomized to the intervention group who received 0.6 mg/kg tPA plus eptifibatide (135 mcg/kg bolus and a 2-hour infusion at 0.75 mcg/kg per minute) and the control group who receive 0.9 mg/kg tPA. The 90day mRS 0–2 was 49.5% vs 26% with odds ratio of 1.74 (95%CI 0.7–4.3, P=0.23). The study demonstrated that enhanced dosing regimen of medium-dose tPA combined with a bolus followed by a short infusion of eptifibatide studied in this trial proved to be safe compared with standard-dose tPA. [21, Rank 3]

Thrombolysis plus transcranial Doppler (TCD) ultrasound

Experimental and clinical studies have consistently demonstrated the capability of ultrasound to enhance enzymatic thrombolysis. Ultrasound application increases the transport of tPA into the thrombus, promotes the opening and cleaving of the fibrin polymers, and improves the binding affinity of tPA to fibrin. While low frequency ultrasound in tandem with tPA has been found to increase the risk of brain hemorrhage, high frequency ultrasound of the type used in standard diagnostic studies has appeared safe and potentially beneficial. Higher frequency ultrasound with microbubble seem to induces further acceleration thrombolysis resulting even more complete recanalization in large-vessel occlusive stroke.

Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) is a phase 2 multicenter randomized trial, demonstrated that 2-h continuous application of 2 MHz transcranial Doppler (TCD) ultrasound in tandem with tPA is safe and may improve outcome. Among 126 patients randomized to tPA plus 2-h TCD monitoring (target group) or tPA alone (control group), symptomatic ICH occurred in 4.8% of target and 4.8% of control patients. Complete recanalization or dramatic clinical recovery at 2 h after tPA bolus was observed in 49% of target and 29% of control patients (P = 0.02). The study demonstrated that continuous TCD ultrasound augments t-PA-induced arterial recanalization, with a nonsignificant trend toward an increased rate of recovery from stroke, as compared with placebo.

A major drawback of the stand diagnostic TCD ultrasound is that it is operator dependent, required a skilled sonography to position the ultrasound window over the target clot. An ongoing trial, CLOTBUST-HF (Hands-Free) will instead test a novel, continuous wave Doppler device that can be placed by any health professional. The clot disrupting effects of ultrasound energy can be potentiated by the addition of gaseous microsphere ultrasound contrast agents, which resonate, expand, oscillate, and detonate near and within the thrombus when subjected to externally applied ultrasound. In the feasibility study, the hands-free TCD device was well tolerated by stroke-free volunteers and did not cause any neurological dysfunction nor did it affect blood brain barrier integrity. If the trials turn out to

be positive, it may offer a novel means to enhance thrombolysis in prehospital settings. [18, Rank 3]

Use of Intravenous tPA in patients with Stroke

Thrombolysis in the Elderly

After age of 55 years, the risk of having AIS doubles for every additional 10 years of life. AIS-related in-hospital mortality was 1–2 times higher in those ages older than 80 or 90 years according to the report from the Get with the Guidelines. The risk of sICH also increased after intravenous tPA in AIS patients older than 80 years old. However, a meta-analysis still revealed that intravenous tPA reduced 3-month mortality in patients >80 years. The rate of sICH in older patients with AIS may vary by different criteria. When using the ECASS criteria, multiple observational studies found no increased risk of sICH in elderly patients post intravenous tPA. However, the rate of sICH doubled in patients older than 80 years post intravenous tPA in NINDS trial. A recent meta-analysis showed no significant difference post intravenous tPA comparing AIS patients ≥80 years with those <80 years. [17, rank 5]

The Issue of Stroke Severity and Stroke Subtypes

Severe Stroke

For severe stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset. However, it was one of the contraindications for the 3–4.5 hour time window in ECASS 3. The severity of stroke at baseline is the strongest predictor of future functional independence or mortality in patients after their first AIS. Subgroup analysis of NINDS studies found that patients with severe strokes could still benefit from IV with a favourable outcome comparing with those not treated. Patients with severe strokes had a higher rate of haemorrhagic transformation and in these patients, haemorrhage might not be related to the use of intravenous tPA. The evidence is insufficient to not offer intravenous tPA to patients with severe strokes or early signs of infarction. Patients with severe stroke and early ischaemic changes on CT was not a contraindication for intravenous tPA. [14, rank 5]

Mild Stroke

NINDS studies did not list the lower limit of the NIHSS score for using intravenous tPA. Several meta-analysis have found that patients with mild stroke were still significantly disabled at 3 months. Such disability could be from motor deficits, cognitive impairment, fatigue or depression, which could not be assessed by NIHSS. Since then, the ENCHANTED trial has also included patients with mild strokes between 3 and 4.5 hours of onset. Although the trial did not reach its predetermined non-inferiority hypothesis, intravenous tPA 0.6 mg/kg showed some efficacy but less haemorrhage in this subgroup. Rapid improvement and mild stroke were two main reasons of why thrombolysis was not given. The treatment should not be delayed due to the improvement of symptoms, while the

treatment time window missed. Thrombolytic therapy should be given as early as possible. [15, rank 3]

Treatment Recommendations

- For Acute Ischemic Stroke (AIS) patients with severe stroke symptoms, intravenous tPA is recommended within 3 hours of symptom onset. Although risk of haemorrhagic transformation may increase, there is still proven clinical benefit (Class I, Level of Evidence A). For patients with mild but disabling stroke, intravenous tPA is indicated within 3 hours of onset (Class I, Level of Evidence A).
- For patients with mild but non-disabling stroke within 3 hours of onset, intravenous tPA might be administrated (Class IIb, Level of Evidence C). For AIS patients with moderate or severe stroke however clinically improving but still have neurological deficit, intravenous tPA is recommended (Class IIa, Level of Evidence A).
- Onset to treatment time is a main factor predicting the outcome; therefore, continuing to observe patient and delay the treatment with intravenous tPA is not recommended (Class III, Level of Evidence C).
- Intravenous tPA treatment is indicated in patients with early ischaemic changes on CT stroke and within the tPA time treatment window (Class I, Level of Evidence A).
- Intravenous tPA is reasonable for patients with moderate to severe ischaemic stroke and early improvement but remain moderately impaired and potentially disabled (Class IIb, Level of Evidence C).
- Intravenous tPA is not recommended to patients with extensive hypodense lesion on CT scan. Extensive hypodense lesions may predict that the damage of brain is irreversible (Class III, Level of Evidence A).
- For patients with mild but disabling stroke symptoms, intravenous tPA is indicated within 4.5 hours of symptom onset (Class IIb, Level of Evidence A). Treatment of patients with mild ischaemic stroke symptoms that are judged as non-disabling may be considered, but the benefit is unclear. [11, Rank 3]

Intravenous tPA in patients with previous use of antithrombotic agents

Patients who had a stroke are often on antithrombotic agents, oral anticoagulants, heparin or low molecular weight heparin (LMWH) and/or recent treated with of tPA. A small retrospective study explored the safety of thrombolysis in patients on antiplatelet agents and found that the risk of sICH was not increased, but parenchymal ICH rate rose substantially. One retrospective study in China found potential risk of sICH in patients on antiplatelet therapy. One large randomised controlled study reported that patients on antiplatelet agents had a trend of developing haemorrhage but without statistical significance, which was supported by meta-analysis findings.

According to the previously published guidelines and drug information, INR >1.7 or PT >15 s in AIS patients with onset of <3 hours were two contraindications for intravenous tPA. In

addition, regardless of the value of INR, it would be contraindicated if a patient was on anticoagulant. One large registry study demonstrated that warfarin increased the risk of sICH. However, after adjustment for stroke severity, age and comorbidities, the risk of sICH was not increased if INR was in the therapeutic range. Compared with unfractionated heparin, LMWH does not prolong PTT but has more biological activity and longer duration of action. Therefore, patients on LMWH within 24 hours of onset of stroke are not suitable for intravenous thrombolytic therapy due to increased risk of haemorrhage.

Direct thrombin inhibitors (dabigatran and argatroban) have become the first-line treatment for stroke prevention in patients with non-valvular atrial fibrillation or peripheral vascular disease. A prospective study of 65 patients who received combination of intravenous argatroban and tPA found that the rate of recanalisation rate was 61% and rate of haemorrhage was 4.6%. Idarizumab, as the antidote of dabigatran, can block the action of dabigatran in several minutes. After careful consideration and reversal of dabigatran with idarizumab, intravenous tPA could be given. PT and aPTT could be prolonged in patients on oral FXa inhibitors (apixaban and rivaroxaban). Even with normal aPTT, INR, platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assays, or no history of receiving these non-vitamin K oral anticoagulants in the past 48 hours (assuming renal function is normal), the efficacy and safety of intravenous tPA remains unclear. [7, Rank 3]

Conclusion

Stroke remains a leading cause of death and disability in the world. Over the past few decades our understanding of the pathophysiology of stroke has increased, but greater insight is required to advance the field of stroke recovery. Clinical treatments have improved in the acute time window, but long-term therapeutics remain limited. Complex neural circuits damaged by ischemia make restoration of function after stroke difficult. New therapeutic approaches, including cell transplantation or stimulation, focus on reestablishing these circuits through multiple mechanisms to improve circuit plasticity and remodeling. Other research targets intact networks to compensate for damaged regions. [7, Rank 5]

References

1. Latoszek-Berendsen A, Tange H, van den Herik HJ, Hasman A. From clinical practice guidelines to computer-interpretable guidelines: a literature overview. Methods Inf Med. 2012
2. Sutton DR, Fox J. The syntax and semantics of the PROforma guideline modeling language. J Am Med Inform Assoc. 2013
3. Shahar Y, Miksch S, Johnson P. An intention-based language for representing clinical guidelines. Proc AMIA Annu Fall Symp. 2016

4. Hripcsak G. Arden syntax for medical logic modules. MD Comput. 2013
5. Wang D, Peleg M, Tu SW, Boxwala AA, Ogunyemi O, Zeng Q, Greenes RA, Patel VL, Shortliffe EH. Design and implementation of the GLIF3 guideline execution engine. J Biomed Inform. 2014
6. Quaglini S, Stefanelli M, Cavallini A, Micieli G, Fassino C, Mossa C. Guideline-based careflow systems. Artif Intell Med. 2015
7. Tu SW, Campbell JR, Glasgow J, Nyman MA, McClure R, McClay J, Parker C, Hrabak KM, Berg D, Weida T, Mansfield JG, Musen MA, Abarbanel RM. The SAGE guideline model: achievements and overview. J Am Med Inform Assoc. 2015
8. Greenes RA, editor. Clinical Decision Support: The Road Ahead. Burlington, MA, USA: Academic Press; 2016.
9. Wang D, Peleg M, Tu SW, Boxwala AA, Greenes A, Patel VL, Shortliffe EH. Representation primitives, process models and patient data in computer-interpretable clinical practice guidelines: a literature review of guideline representation models. Int J Med Inform. 2015
10. Isern D, Moreno A. Computer-based execution of clinical guidelines: a review. Int J Med Inform. 2013
11. Zhou L, Karipineni N, Lewis J, Maviglia SM, Fairbanks A, Hongsermeier T, Middleton B, Rocha RA. A study of diverse clinical decision support rule authoring environments and requirements for integration. BMC Med Inform Decis Mak. 2013
12. Gray BH, Bowden T, Johansen I, Koch S. Electronic health records: an international perspective on “meaningful use” Issue Brief (Commonw Fund) 2014
13. International Organisation for Standardisation (ISO), ISO TC 215/WG 1. ISO/TR 20514: health informatics – electronic health record – definition, scope and context. Tech Rep. 2015.
14. Goossen W, Goossen-Baremans A, van der Zel M. Detailed clinical models: a review. Health Inform Res. 2013
15. Chen R, Georgii-Hemming P, Åhlfeldt H. Representing a chemotherapy guideline using openEHR and rules. Stud Health Technol Inform. 2013
16. Lezcano L, Sicilia MA, Rodríguez-Solano C. Integrating reasoning and clinical archetypes using OWL ontologies and SWRL rules. J Biomed Inform. 2011
17. Barretto SA. PhD Thesis. Adelaide: University of South Australia, School of Computer and Information Science; 2015. Designing guideline-based workflow-integrated electronic health records.
18. Anani N, Chen R, Prazeres Moreira T, Koch S. openEHR-based representation of guideline compliance data through the example of stroke clinical practice guidelines. Stud Health Technol Inform. 2012
19. Peleg M. Computer-interpretable clinical guidelines: a methodological review. J Biomed Inform. 2013

20. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2013.
21. Ford GA, Ahmed N, Azevedo E, Grond M, Larrue V, Lindsberg PJ, Toni D, Wahlgren N. Intravenous alteplase for stroke in those older than 80 years old. Stroke. 2010
22. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, Parsons M, Roine RO, Toni D, Ringleb P. SITS investigators. Implementation and outcome of thrombolysis with alteplase 3–4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol. 2010
23. Sordo M, Boxwala AA, Ogunyemi O, Greenes RA. Description and status update on GELLO: a proposed standardized object-oriented expression language for clinical decision support. Stud Health Technol Inform. 2014
24. Mei J, Liu H, Xie G, Liu S, Zhou B. An OCL-compliant GELLO engine. Stud Health Technol Inform. 2011
25. Koutkias V, Lazou K, de Clercq P, Maglaveras N. Towards a standardised representation of a knowledge base for adverse drug event prevention. Stud Health Technol Inform. 2011
26. Panzarasa S, Quaglini S, Micieli G, Marcheselli S, Pessina M, Pernice C, Cavallini A, Stefanelli M. Improving compliance to guidelines through workflow technology: implementation and results in a stroke unit. Stud Health Technol Inform. 2016
27. Mei J, Liu H, Xie G, Lakshmanan GT. An engine for compliance checking of clinical guidelines. Stud Health Technol Inform. 2012
28. Luker J, Grimmer-Somers K. Factors influencing acute stroke guideline compliance: a peek inside the 'black box' for allied health staff. J Eval Clin Pract. 2015
29. Albakri EA, Richards F III, Hall M, Dion C, Miranda LS, Turkel R, Sand C, Vasey P, McDonald K, Michelman M, Smith Z, Davison K, Pfannerstill L. Cooperative efforts improve compliance with acute stroke guidelines. South Med J. 2014
30. LaClair BJ, Reker DM, Duncan PW, Horner RD, Hoenig H. Stroke care: a method for measuring compliance with AHCPR guidelines. Am J Phys Med Rehabil. 2011