Advances in Stroke Over the Past Decade

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ABSTRACT

Over the last decade, a number of advances in the care of stroke and TIA patients have been made. These advances include prevention, acute management, and recovery. Some of this work has occurred in Rhode Island. This review will focus on the revised definition of stroke and TIA; short-term risk of TIA; rapid management of TIA; targeted use of medication and lifestyle changes; monitoring for atrial fibrillation; novel anticoagulants for atrial fibrillation; a better understanding of the limitations of intra-arterial therapy for acute ischemic stroke; clinical treatment trials for intracerebral hemorrhage; and the use of robotic, magnetic, and chemical interventions to improve function after stroke.

KEYWORDS: Stroke, TIA, risk factors, acute intervention, recovery

INTRODUCTION

In this brief review, some of the advances in stroke over the past decade will be reviewed. Of note, many of these advances occurred as a result of work done here in Rhode Island.

DEFINITION OF STROKE AND TIA

The definitions of stroke and transient ischemic attack (TIA) have evolved over the last decade. The term TIA was first used in the 1960s to designate a presumed ischemic neurologic event from which a complete recovery occurred in under 24 hours. In 2002, a panel of experts proposed a new, tissue-based, definition of TIA: "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction." In 2009, the American Stroke Association proposed a modification of that definition which eliminated time altogether and also included spinal cord ischemia as follows: "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (on neuroimaging)."[1]

The basis for the change in these definitions comes from research over the last decade. Among 19 studies of 1,117 patients with the time-based definition of TIA, the rate

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of positive findings on diffusion-weighted imaging (DWI) was 39%.[1] DWI is an MRI sequence sensitive to the diffusion of water molecules. During acute ischemic stroke, there is a restriction of the normal Brownian movement of water which manifests as brightness on DWI. The longer the event, the more likely DWI will be positive. Nevertheless, short-lasting events can also result in a positive DWI. As imaging technology evolves, smaller areas of suspected tissue damage will also become apparent, further increasing the percentage of patients who are reclassified as having had a stroke. Indeed, it is possible that all such events cause some tissue damage and would be obvious if we had the capability of performing non-invasive microscopic imaging.

SHORT-TERM RISK AFTER TIA AND ITS MODIFICATION

Though it was well known that stroke carried a substantial risk of recurrence, it was not until a study in 2000 that the high short-term risk of TIA became apparent.[2] In that study, which used the 24-hour definition of TIA, approximately 10% of patients returned with stroke within 90 days, half within the first 48 hours. Patients in that study did not have

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Robotic training enhances arm motor recovery after stroke.

urgent evaluation or treatment. A risk-stratification model called ABCD2 was then developed which allocated points for presenting variables (age, blood pressure at presentation, clinical symptoms, duration, diabetes).[3] The range of scores is 0-7 with higher scores being associated with greater risk.

The finding of high risk of stroke following TIA led to clinical studies evaluating urgent intervention. The first study, called SOS-TIA, and conducted in France, evaluated an urgent management program including rapid carotid imaging, rhythm monitoring, carotid revascularization when appropriate, anticoagulation when appropriate, and lipid management.[4] Compared with the expected rate of stroke (based on ABCD2 risk stratification), the authors found an approximate 80% reduction in risk. Simultaneously, the EXPRESS study, conducted in England, using a before-and-after design, found a similar 80% reduction in stroke recurrence using a rapid evaluation and treatment program.[5] A 2012 study from Australia demonstrated a 1.5% risk of stroke at 90 days in patients with TIA who had all investigations and management conducted in the emergency department.[6] The expected rate, based on the ABCD2 scheme, was 10%.

On the basis of these findings, Rhode Island Hospital developed a TIA unit in the emergency department in March 2013. The rate of stroke at 7 days, based on telephone contact, has been less than 1% to date.

LONG-TERM RISK MODIFICATION

INTERSTROKE was a landmark case-control study which matched 3,000 stroke patients with 3,000 controls in 22 countries.[7] The authors found that 10 risk factors were associated with 90% of all stroke [hypertension, current smoking, increased waist-to-hip ratio, poor diet, physical inactivity, diabetes mellitus, excessive alcohol intake, psychosocial stress and depression, cardiac causes and abnormal ratio of apolipoproteins B to A1. The authors concluded that interventions that targeted these factors could substantially reduce the burden of stroke. The newly formed School of Public Health at Brown University will focus on initiatives at improving risk factors that lead to cardiovascular disease. A recent study by Wing and colleagues at Brown University found that the addition of intensive lifestyle changes (diet and exercise) did not reduce the rates of death, stroke, or myocardial infarction compared with medication use alone.[8] However, those assigned to intensive lifestyle changes used less medication.

Additional advances in the last decade include the observation that longer heart rhythm monitoring leads to an increased detection of atrial fibrillation. In a Canadian study which randomly assigned patients to Holter monitoring versus 30 day monitoring in patients with cryptogenic stroke, detection rates of atrial fibrillation were 3% and 16%, respectively.[9] What is unclear is what duration of atrial fibrillation on these monitors confers increased risk. For example, does a 20-second episode of atrial fibrillation during 30 days of monitoring suggest increased risk requiring anticoagulation? The standard definition of paroxysmal atrial fibrillation is at least 30 continuous seconds of the abnormal rhythm. Further study will be required to determine prognosis and optimal medical treatment. There are now many options for anticoagulation for patients with atrial fibrillation including vitamin K antagonists (warfarin), direct thrombin inhibitors (dabigatran), and factor Xa inhibitors (apixaban, rivaroxaban).[10] These agents can be expected to reduce the risk of embolism by approximately 60%-70% relative to no treatment and approximately 40%-50% relative to aspirin. Individualized determination of risk can be accomplished with the CHADS2 and CHA2DS2Vasc scoring systems.[11] Specific risk assessment for neurovascular processes may be helpful in shared decision-making processes, with careful attention to presentation format.

At this time, there does not appear to be a role for anticoagulation in intracranial atherosclerosis, cervical arterial dissection, or patent foramen ovale (PFO)-related stroke. Recurrence risk of stroke is highest with intracranial atherosclerosis (approximately 12% per year) and much lower with PFO-related stroke (approximately 1%–2% per year), and cervical arterial dissection (3% in the 12 months after ictus). In addition, interventional approaches do not appear to mitigate risk in these conditions, and even if subgroup analyses suggest benefit, the absolute reduction is very small (less than 1%) with an increased risk of procedure-related complications.

ACUTE INTERVENTIONS

Despite the wide use of intra-arterial procedures for the treatment of acute stroke, definitive evidence of overall benefit is lacking at this time. Three trials failed to show net benefit for intra-arterial therapy added to intravenous thrombolytic therapy within 3 hours (IMS III), intra-arterial compared to intravenous therapy within 4.5 hours (SYNTHESIS), and imaging-guided intra-arterial therapy compared to placebo within 8 hours (MR RESCUE).[12] Post-hoc analyses suggest that there are subgroups which may benefit. The most important variable is time to treatment. There is a strong correlation between time to intra-arterial recanalization and outcome.[13] Further, the completeness of recanalization at earlier time points is also important.[14] Because approximately 2 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers are lost every second during a large vessel ischemic stroke,[15] recanalization at late time points may only serve to perfuse already destroyed tissue, analogous to putting out a fire after a house has already burned down.

Intracerebral hemorrhage carries a worse prognosis than ischemic stroke yet an acute treatment which improves outcome remains elusive. Potential promising interventions include rapid control of blood pressure and targeted removal of clot. The INTERACT2 study failed to show a statistically significant benefit in favor of rapid blood pressure reduction

below a target of 140 mmHg systolic within the first 6 hours of bleeding but sample size may have precluded detection of benefit.[16] The ongoing ATACH-II study,[17] which is also evaluating rapid reduction in blood pressure to less than 140 mmHg systolic should yield a definitive answer on the question of blood-pressure reduction, particularly when data are pooled with INTERACT2.

Another intriguing option for the treatment of intracerebral hemorrhage is thrombolysis-assisted clot evacuation. The procedure consists of creation of a burr hole ipsilateral to the bleeding, insertion of a catheter into the center of the clot, injection of tPA into the center of the clot, and then evacuation of the dissolved material. Moreover, the procedure can be performed as late as 24 hours. MISTIE II was a small study which suggested benefit of this procedure with good recovery at one year, reduced length-of-stay in the hospital, and total cost of care.[18] Mortality, however, was not decreased. MISTIE III,[19] the phase III version of the study, will provide a definitive answer on whether this procedure is truly of value in the case of patients with intracerebral hemorrhage.

RECOVERY OPTIONS

Recovery after stroke is an exciting area of research opportunity. The notion that the nervous system was incapable of regeneration was dispelled in the 1990s. Since that time, a number of potential interventions to augment recovery after stroke have been posited. These include robotic, electromagnetic, and pharmacological therapies. Cellular therapy remains an active area of interest but logistical and regulatory issues in the United States have not led to a trial in stroke at this time. In addition, the concept that electrical energy from the brain can be converted to kinetic action through an external device has now become a reality.

Lo and colleagues, from the Providence VA, published a randomized trial of robot-assisted therapy for upper-limb impairment in stroke in 2010.[20] It was the first such study ever published in the *New England Journal of Medicine*. Though the study did not find that robot-assisted therapy was superior to intensive or usual care at 12 weeks, there was a suggestion of benefit over usual care at 36 weeks. Since then, the research group at the VA has continued to explore different robot options for the purpose of augmenting limb recovery.

Hochberg, Donoghue and colleagues from the Brown Institute of Brain Sciences made headlines worldwide with the publication of an article in *Nature* regarding the implantation of a 96-channel microelectrode array that allowed two patients with long-standing tetraplegia to control an external robot arm.[21] In one patient, the arm was used to lift a bottle of coffee to her mouth. Remarkably, the complex robotic arm movements could be controlled by a very small pool of neurons. This groundbreaking research paves the way for next-generation devices that can be controlled through implanted chips.

Multiple studies now suggest that transcranial magnetic stimulation (TMS) may be used to augment both motoric and linguistic recovery after stroke. Of note, excitatory stimulation of the affected hemisphere appears to produce benefit while inhibitory stimulation of the unaffected hemisphere may produce benefit.[22] A transcranial magnetic stimulation device now exists at Butler Hospital and will allow additional study in this area.

Pharmacological therapy, such as fluoxetine and PDE5 inhibitors, are also of potential benefit. The FLAME study suggested that fluoxetine not only improved depression but also improved motor function after stroke.[23] Sildenafil has been shown in young and aged animals to improve neurological outcome though neurogenesis, angiogenesis, and synaptogenesis.[24,25] Preliminary human studies[26] have served as the basis for larger pilot randomized trials.

SUMMARY

Evolving understanding of the concept of cerebral ischemia and recurrent risk has led to improved treatments and short-term outcomes for patients. Large international studies of recurrent stroke have now helped focus the agenda for what needs to be done to lower long-term risk. Beneficial acute treatments of both ischemic and hemorrhagic stroke continue to be defined and many exciting options are now available. Strategies for improving recovery after disabling stroke are now entering an active phase of development. Rhode Island, the Brown Institute for Brain Sciences, and the Norman Prince Neurosciences Institute have the tools and expertise to be leaders in these areas.

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Disclosures

The author reports no conflicts of interest.

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