Interventional Stroke Therapy: Current State of the Art and Needs Assessment

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The primary therapeutic strategy for ischemic stroke, as for MI patients, is early reperfusion. Improvement in stroke treatment will require dedicated stroke centers to emulate MI quality indicators such as minimizing the “door-to-balloon time”. A critical element in achieving this goal will be organizing the existing multidisciplinary pool of carotid interventionalists to provide the endovascular component of the acute care for ischemic stroke patients.

Key words: peripheral vascular disease (PVD); stroke; thrombolytic

INTRODUCTION

Each year almost three-quarters of a million people experience a stroke [1]. Stroke accounts for approximately 1 of every 16 deaths in the United States. The estimated direct and indirect cost of stroke for 2007 is $62.7 billion. Stroke ranks as the number-one cause of adult disability in the United States [2]. The vast majority of strokes (87%) are ischemic in nature. Ischemic stroke is amenable to reperfusion therapy; however, the benefit for reperfusion therapy, as for treatment of myocardial infarction (MI), is time-limited.

It is important to appreciate the similarities and understand the differences between ischemic stroke and MI. Both stroke and MI are ischemic events that are modified by individual patient factors, which are usually unknown upon the patient’s initial evaluation, such as the total vascular disease burden and adequacy of the collateral circulation (e.g., patency of the Circle of Willis and pial collaterals). These factors result in a highly variable and unpredictable margin of viable brain tissue that surrounds the irreversibly injured tissue (e.g., the ischemic penumbra). The key pathological difference between the two is that MI is usually the result of plaque rupture and in-situ thrombosis, whereas ischemic stroke most often results from athero-thrombotic embolism [3]. The goal of therapy in ischemic stroke is to safely maximize patient functional recovery by rapidly reperfusing the ischemic penumbra.

EVALUATION AND TREATMENT

Because the therapeutic window for treating acute stroke is so narrow, <3 hr from stroke onset to achieve benefit with intravenous (IV) thrombolysis, and <6–8 hr for endovascular therapy, prompt evaluation and initiation of treatment is critical [4,5]. Analogous to strategies...
formulated to expedite treatment of MI, pathways for rapid evaluation of potential stroke patients are recommended for emergency departments so that stroke treatment can be initiated without delay. The initial patient contact should determine the time of stroke onset, assess the clinical deficit using the uniform National Institutes of Health Stroke Scale (NIHSS), and perform a basic laboratory evaluation.

Brain imaging with computed tomography (CT) or magnetic resonance (MR) is a required element for evaluation of acute stroke patients to rule out hemorrhage [4]. Brain tissue at risk for ischemic injury is determined with MR perfusion-weighted imaging, and brain tissue that has been irreversibly damaged can be assessed with MR diffusion-weighted imaging [4]. Because of time constraints, some centers are adopting the more readily available, easy to use, and more rapidly performed CT perfusion scan for this purpose. If the brain tissue at risk for ischemic injury is equal to the amount of brain tissue that has been irreversibly damaged, then a “matched” condition exists. In patients with matched or balanced defects, thrombolysis may offer marginal benefit but still exposes the patient to the risk of intracerebral hemorrhage from the thrombolytic agent. However, if the brain tissue at risk (e.g., the ischemic penumbra) is larger than the irreversibly damaged brain, then a “mismatch” exists with a risk-to-benefit ratio that favors reperfusion therapy. Current data suggest that 20% of major stroke patients will exhibit a matched defect, whereas 80% will have a mismatch that is favorable for reperfusion within the first 6–8 hr [6].

**Intravenous Lysis**

IV administration of rt-PA (0.9 mg/kg, maximum dose 90 mg) has been clearly demonstrated to benefit patients, who are not at increased bleeding risk, and who present within 3 hr of the onset of ischemic stroke. IV thrombolysis with rt-PA is a Class I, Level of Evidence “A” recommendation, from the most recent American Heart Association guideline document, and is the preferred therapy for selected patients who present with ischemic stroke within the 3-hr window despite the fact that nationally only 2% of all ischemic stroke patients actually receive this therapy [4,7].

The institution of general supportive care, including blood pressure, glucose, and temperature control, is indicated in addition to the administration of thrombolytic agents. In a large randomized trial of IV therapy (rt-PA) compared to placebo in patients presenting within 3 hr of onset, there was no difference in outcomes between the groups at 24 hr [8]. After 3 months of follow-up, the percentage of patients who achieved full recovery was 21% for the placebo group and 34% for the rt-PA group (P < 0.05). However, there was no difference in mortality between the two groups. The intracranial bleeding rate was 10-fold greater (6.4% rt-PA vs. 0.6% placebo, P < 0.001) in the rt-PA group compared to placebo. The incidence of intracranial hemorrhage when IV thrombolysis is used for acute stroke is increased in patients with larger strokes and those treated later than 3 hr [9]. There is also evidence that patients who have intracranial internal carotid occlusion or proximal (M1 segment) occlusion of the middle cerebral artery have a poor prognosis even with IV thrombolysis [4].

The use of IV rt-PA has been supported as a strategy for reducing stroke costs, recognizing it as a treatment associated with important health gains (4 to 6 quality-adjusted life-years gained over a lifetime per 100 patients treated) and both short- and long-term cost savings [10,11]. Despite this, the implementation of this therapy is not widespread, as it is estimated that IV thrombolytic therapy is used in only 2% of all ischemic stroke patients [7,12]. One reason may be that the median time from stroke onset to arrival in most emergency departments is between 3 and 6 hr. Improved clinical outcomes at 3 months were seen only for patients with acute ischemic stroke when IV thrombolytic treatment was started within 3 hr of the onset of symptoms. Of patients with ischemic stroke in the California Acute Stroke Pilot Registry, only 23.5% arrived at the emergency department within 3 hr of symptom onset, and only 4.3% received thrombolysis [13]. A population-based study in a biracial population of 1.3 million patients in Ohio between 1993 and 1994 showed that only 8% of all ischemic stroke patients presented to an emergency department within 3 hr of onset and met other eligibility criteria for rt-PA. However, despite the established benefit for “on-label” IV rt-PA in acute ischemic stroke, if it is used outside the guidelines (i.e., >3 hr), the risk of complications is significantly increased [14–16].

**Catheter-Based Therapy**

Intra-arterial thrombolysis is of benefit in selected patients if administered within 6 hr of the onset of stroke. The Class I recommendation from the most recently updated stroke guidelines states that intra-arterial thrombolysis should be performed at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists [4].

The Prolyse in Acute Cerebral Thromboembolism Trial (PROACT II), with a median time to treatment of 5.3 hr, randomized patients with a major neurological deficit (NIHSS = 18) and demonstrated poor outcomes for conservative therapy versus intra-arterial thrombolysis [17]. PROACT II demonstrated a beneficial effect for intra-arterial thrombolysis up to 6 hr af-
ter stroke onset in 180 patients with occlusions of the middle cerebral artery. However, in the PROACT II study, patients were highly selected with over 10,000 patients screened to find 480 patients eligible for angiography, of whom only 180 patients with proximal middle cerebral artery (M1 or M2 segment) occlusion were randomized.

The MERCI [5,18] and Multi-MERCI [19] trials reported the results of mechanical thrombo-embolectomy using the Merci\textsuperscript{R} Retriever (Concentric Medical, Mountain View, CA). These prospective, controlled, single-arm trials evaluated mechanical thrombo-embolectomy in acute stroke patients within 8 hr of presentation who had angiographically confirmed large-vessel occlusion (carotid terminus, middle cerebral (M1, M2), and vertebrobasilar arteries) in a broad cohort (no upper age or NIHSS limits). Multi-MERCI included use of the next-generation retriever and widened inclusion criteria to permit mechanical thrombo-embolectomy in patients who had failed IV t-PA. In the MERCI trial, 60.3% (85/141) of patients achieved postprocedure revascularization. In Multi-MERCI, 68.3% (112/164) achieved postprocedure revascularization. It is encouraging that both trials demonstrated significantly better 90-day outcomes (functional outcomes and mortality) among successfully revascularized patients compared with nonrevascularized patients.

**STROKE CENTERS**

To improve stroke care, the Brain Attack Coalition has recommended the development of Primary Stroke Centers (PSCs) [20] and Comprehensive Stroke Centers (CSCs) [21].

- PSCs are designed to deliver basic stroke care, including treatment with IV thrombolysis, and ongoing care for uncomplicated stroke patients with the ability to admit patients to a designated stroke unit staffed with specialized personnel.
- CSCs provide advanced care to stroke patients, offering endovascular intervention and care for more complicated patients requiring specialized intensive care unit placement. The recommended staffing for the CSCs is outlined in the comprehensive consensus statement and specifically include interventional physicians with expertise in cervico-cerebral procedures and techniques [21].

While national estimates of IV rt-PA use for acute ischemic stroke continue to be disappointingly low (2%) [7], there are examples of communities that have successfully developed stroke centers with dramatic improvements in proportions of rt-PA-treated stroke patients [7,22–24]. Despite this, there is an estimated ceiling of 22% of patients who would be candidates for on-label rt-PA use in ischemic stroke, leaving a large majority of patients as potential candidates for invasive or interventional stroke therapy [7]. In patients who are not candidates for IV thrombolysis, the outcome for interventional therapy, in case series and uncontrolled trials, appears to be favorable [25]. Since there is an average net cost savings and quality-of-life improvement for each patient receiving stroke therapy, even small increases in the proportion of ischemic stroke patients who receive reperfusion therapy would result in an enormous savings for the healthcare system [7].

**MANPOWER**

It is clear that the benefits of CSCs include improvement in stroke mortality in hospitals with stroke neurologists and a stroke team [26] and that specialized stroke services improve outcomes for stroke patients. Current Level I guidelines encourage development of both PSCs and CSCs that will be capable of being certified by an external accrediting body [4]. It is also recommended that ambulances bypass hospitals that do not have specialized and dedicated resources to treat stroke patients and to go to the closest facility capable of providing acute stroke care (Class I, Level of Evidence “B”) [4].

Currently, the process of developing PSCs is ahead of the development of CSCs [4]. However, it is clear that the ability of the CSC to offer an intra-arterial, endovascular approach to patients who are not candidates for IV therapy has the advantages of delivering a high concentration of drug directly to the clot, thereby reducing systemic exposure to the lytic agent. This invasive approach may be performed in conjunction with mechanical disruption of the thrombus to facilitate reperfusion. Also, the recent approval of a mechanical clot-retrieval device (MERCI\textsuperscript{R}, Mountain View, CA) for acute stroke treatment offers an additional tool for the interventionalist to improve recanalization while minimizing the hemorrhagic risk [5].

One of the major problems limiting the growth of CSCs is availability of skilled interventionalists to provide 24-hr-a-day, 7-days-a-week, 365-days-a-year support for acute stroke intervention [27]. Although cervico-cerebral interventional therapies for ischemic stroke offer promise as a means to extend the time window available for acute treatment, their widespread application may be constrained by the limited availability of skilled neurointerventionalists and sophisticated endovascular suites. A recent survey identified a total of only 385 interventional neuroradiologists in the US, practicing in 238 hospitals covering 45 states [27]. Five states had no interventional neuroradiologists. Stretched that thin, there is no way this small number of narrowly specialized physicians can
provide on-demand stroke intervention within 6 hr to patients who are not candidates for IV thrombolytic therapy. Currently, there is a manpower crisis for providing endovascular therapy for acute stroke.

A starting place to correct this patient access problem is among the rapidly expanding, multispecialty community of carotid interventionalists. There has been a surge in the number of physicians from multiple specialties performing carotid artery stenting [28–30]. A worldwide breakdown of carotid stent practices by specialty reveals that 58% are cardiologists, 25% are radiologists, and 17% are vascular surgeons [29].

In addition to endovascular stent placement and emboli protection skills, competence for carotid stenting requires knowledge of neuroanatomy, the skill to cannulate cervical vessels and perform selective cerebral angiography and the ability to perform neurovascular rescue. Neurovascular rescue is a clear example of endovascular stroke therapy already being performed by these physicians. While many of these operators are prepared to perform stroke intervention, they are simply not engaged in an organized manner to provide on-demand endovascular stroke therapy. Each of these skilled carotid endovascular interventional operators, with assistance and mentorship from stroke neurologists, neurosurgeons, neuroradiologists and others, is a potential stroke interventionalist. We suggest taking what has been learned in treating MI and applying it to “brain attacks,” utilizing a multidisciplinary approach.

SUMMARY

The primary therapeutic strategy for ischemic stroke, as for MI patients, is early reperfusion. Although there may be other modifying factors (e.g., pharmacological and hypothermia) to reduce brain injury, the cornerstone of ischemic stroke therapy is early reperfusion therapy with IV thrombolytic therapy with endovascular therapy reserved for patients who are not candidates for IV thrombolysis. Improvement in stroke treatment will require dedicated stroke centers to emulate MI quality indicators such as minimizing the “door-to-balloon time.”

Not all strokes will benefit from endovascular therapy. Selecting appropriate patients requires reorganizing our healthcare delivery system to provide access to acute stroke care in highly specialized stroke centers. A critical element in achieving this goal will be organizing the existing multidisciplinary pool of carotid interventionalists to provide the endovascular component of the acute care for ischemic stroke patients. We will not realize the full benefit of stroke therapy until each community has the capacity to treat ischemic stroke with the same systematized approach that is used to treat acute MI. Furthermore, until we have an adequate cadre of interventional physicians who can provide on-demand endovascular therapy to selected stroke patients, we cannot institute a “door-to-balloon time” treatment scheme to maximize early stroke reperfusion.

The goal of ischemic stroke therapy is to safely maximize the patient’s functional recovery with early reperfusion to salvage the ischemic penumbra. Because the nature of the atherothrombotic material causing ischemic stroke is likely to result in a larger clot burden often associated with older, more organized thrombus, the response to IV lysis may be less effective than is seen for MI-associated thrombosis. It has been well established that early reperfusion with intervention (door-to-balloon time) is the optimal treatment of MI, and will likely be the optimal treatment for ischemic stroke patients. This treatment strategy cannot be implemented with the current shortage of “neurovascular interventionalists” [27].

Clearly, the current pool of available manpower comes from the current roster of trained carotid stent physicians, including neurologists, surgeons, radiologists, and the largest group, cardiologists, who are already committed to minimizing the “door-to-balloon time” for heart attacks. As we work to develop stroke centers, we need to be organizing and training a group of multidisciplinary stroke interventionists to support a “door-to-balloon time” treatment standard for “brain attacks” while making acute stroke intervention available 24-hr-a-day and 7-days-a-week in stroke centers in every community, as we have done for the treatment of acute MI.

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APPENDIX

The Stroke Roundtable was organized in February 2007 to address the critical need for collaborative, multidisciplinary partnership to conduct research and guidelines development in the area of interventional stroke treatment. The members believe that, because of the dynamic, multidisciplinary nature of this area, the Roundtable must be inclusive, with representatives from all stakeholder medical disciplines, including industry and government policymakers. For more information about the Stroke Roundtable, contact Dr. Christopher Cates at Christopher.Cates@emoryhealthcare.org or 404-712-5990.

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