Controversies in Acute Stroke Treatment

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ABSTRACT

The evidence base supporting the management of patients with acute stroke is evolving at a rapid rate, as new methods that aim to reduce disability and death from stroke are explored. Intravenous tissue plasminogen activator remains the only treatment shown in numerous studies to reduce disability 3 months after stroke with no increase in the risk of death and a relatively minor rate of symptomatic intracerebral hemorrhage complications. Despite these findings, health care providers have been slow to adopt this evidence-based treatment, which results in many patients experiencing disability caused by stroke. Numerous controversies exist related to the management of patients with acute stroke, including the use of tissue plasminogen activator, positioning and early mobility, blood pressure lowering in acute intracerebral hemorrhage, and even the use of innovative advanced practice nurse-led stroke treatment teams, with varying amounts of evidence available to provide direction. This article explores controversies associated with both approved and evolving treatments for ischemic and hemorrhagic stroke and makes recommendations for practice on the basis of the body of existing evidence, with an aim to improve the delivery of acute stroke treatment.

Keywords: acute stroke, advanced practice nurses, intra-arterial treatment, intravenous tissue plasminogen activator (tPA), head-of-bed positioning

In May 1996, the US Food and Drug Administration (FDA) approved the intravenous use of tissue plasminogen activator (tPA) for the treatment of acute ischemic stroke after the successful completion of the National Institutes of Neurologic Disorders and Stroke (NINDS) rt-PA Stroke Study. Despite 15 years of research on tPA, a significant number of clinicians managing acute stroke in the United States remain reluctant to adopt aggressive reperfusion treatment, resulting in rates of tPA administration between 3.4% and 5.2%. However, tPA remains the only treatment of acute ischemic stroke that extensive research has shown to significantly reduce disability with no increase in risk of death. Unfortunately, for patients with intracerebral hemorrhage (ICH), no proven methods have been identified yet to reduce the significant disability caused by this disease.

The rate at which acute stroke research is evolving is staggering considering that this disease was largely ignored for years. However, although promising new discoveries have been made, many significant gaps in knowledge persist, generating many gray areas in practice that can be filled only with theoretically based expert consensus. The slow translation of new stroke evidence into mainstream practice is the most problematic area. This article provides an evidence-based look at controversies in the management of patients with acute stroke.

Treatment of Conditions That Mimic Stroke With Intravenous tPA

Current guidelines from the American Stroke Association (ASA) recommend rapid assessment and diagnosis of patients with acute stroke to achieve a tPA door-to-needle time of no more than 60 minutes, because the benefit of reperfusion treatment is time dependent in most cases. For this timeline of treatment to be achieved, patients must receive prompt triage, a thorough yet succinct neurological examination, and a noncontrast head computed tomography (CT) scan with rapid completion and interpretation. Given that tPA may be administered intravenously for hemorrhage-negative noncontrast CT, the diagnosis of ischemic stroke relies heavily on an accurate history of sudden symptom onset and clinical localization of neurological disability to a discrete neurovascular territory in the brain. However, symptoms resulting from conditions other than stroke that also have sudden onset may mimic ischemic stroke, creating concerns about the authenticity of stroke diagnosis and treatment with tPA.

Controversy 1: What Is the Risk of Treating a Condition That Mimics Stroke With Intravenous tPA?

Stroke mimics are well described in the literature and include seizure with Todd’s paralysis,
Conclusions and Recommendations

tPA treatment of patients with conditions mimicking stroke is relatively uncommon, but when it occurs, these patients do not appear to be at any undue risk. Although clinicians may be suspicious of a condition mimicking stroke, unless a mimic can be rapidly evaluated with diffusion weighted imaging, tPA treatment should not be delayed. “Time Is Brain” continues to be the mantra for early diagnosis and treatment with intravenous tPA, which is associated with a well-documented 30% chance for functional recovery after acute ischemic stroke. Therefore, taking a thorough history and conducting a neurological examination, combined with a negative noncontrast CT scan, are more than sufficient to make a safe tPA treatment decision.

Intravenous tPA Treatment Window

The US FDA has approved the intravenous administration of tPA within the first 3 hours from the onset of acute ischemic stroke. However, in the European Union, Australia, Canada, New Zealand, and many Asian and Middle Eastern countries, intravenous tPA is approved for administration within 4.5 hours from symptom onset in acute ischemic stroke.

Controversy 2: Can Intravenous tPA Be Safely Administered Up to 4.5 Hours From Symptom Onset to Patients With Acute Ischemic Stroke?

Thrombolysis as a treatment for ischemic stroke has been studied since 1958, and early drug and dose-finding trials began in the 1960s and carried on through the early 1990s. Results from multiple tPA trials showed a benefit that wanes with time delays between onset of symptoms and treatment commencement.

The NINDS rt-PA Stroke Study

The NINDS rt-PA Stroke Study demonstrated the benefit of intravenous alteplase (Activase) tPA therapy for patients with ischemic stroke when treatment was initiated within 3 hours of the onset of symptoms with a dose of 0.9 mg/kg with a maximum dose of 90 mg; importantly, the increased benefit in the tPA group was not associated with an increase in death, and the sICH rate in the trial was 6.4%.
The NINDS study used an extremely conservative protocol definition of sICH, “clinical worsening, any deterioration in the patient’s neurological condition,” in combination with any hemorrhage noted on the CT scan. Under this definition, infarct evolution as the cause for worsening, in combination with even small petechial hemorrhages, was counted as symptomatic. Since that time, the definition of sICH has evolved to deterioration associated with worsening of 4 or more points on the NIHSS in combination with parenchymal hemorrhage. Although more hemorrhagic transformation was noted in the tPA group compared with the placebo group in the NINDS study, re-analysis of trial data by Saver and colleagues indicates that 32% of patients who experienced sICH were destined for a fatal outcome even if they had not been treated with tPA, for reasons including cytotoxic edema, infarct expansion, and pneumonia. Today, leading vascular neurologists fervently support the increased use of tPA for acute ischemic stroke, but the low rates of actual tPA treatment in the United States indicate that many providers remain reluctant to use it for treatment.

In 1996, following the release of the results from the NINDS study, the European Medicines Agency approved thrombolysis with alteplase tPA for ischemic stroke, but the approval was granted with 2 conditions:

1. A further randomized trial, the European Cooperative Acute Stroke Study (ECASS-3), extending the therapeutic window beyond 3 hours.
2. The creation of an observational phase IV safety registry, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), to assess the safety profile of alteplase in routine clinical practice within 3 hours of the onset of stroke symptoms.

The SITS-MOST Phase IV Effectiveness Study
Between 2002 and 2006, SITS-MOST recruited 6483 patients from 285 centers in 14 countries in a prospective, open, monitored, observational study. Primary outcomes were sICH (deterioration in NIHSS score of 4 points or greater) within 24 hours and mortality at 3 months. Additional data collected included the original NINDS/Cochrane definition for sICH and functional outcome at 3 months; findings from this phase IV effectiveness study were compared alongside pooled results from relevant randomized controlled trials (Table 1). SITS-MOST confirmed the NINDS study used an extremely conservative protocol definition of sICH, “clinical worsening, any deterioration in the patient’s neurological condition,” in combination with any hemorrhage noted on the CT scan. Under this definition, infarct evolution as the cause for worsening, in combination with even small petechial hemorrhages, was counted as symptomatic. Since that time, the definition of sICH has evolved to deterioration associated with worsening of 4 or more points on the NIHSS in combination with parenchymal hemorrhage. Although more hemorrhagic transformation was noted in the tPA group compared with the placebo group in the NINDS study, re-analysis of trial data by Saver and colleagues indicates that 32% of patients who experienced sICH were destined for a fatal outcome even if they had not been treated with tPA, for reasons including cytotoxic edema, infarct expansion, and pneumonia.

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### Table 1: Comparison of Findings From the SITS-MOST Phase IV Effectiveness Study With Findings From Pooled Randomized Trials of Intravenous tPA for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>SITS-MOST</th>
<th>Pooled Randomized Trials</th>
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</thead>
<tbody>
<tr>
<td>sICH at 24 h</td>
<td>sICH at 7 d</td>
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<tr>
<td><strong>sICH definition:</strong> ≥ 4-point increase on NIHSS with parenchymal hemorrhage</td>
<td><strong>Definition:</strong> ≥ 4-point increase on NIHSS with parenchymal hemorrhage</td>
</tr>
<tr>
<td>• 107 sICH patients</td>
<td>• 40 sICH patients</td>
</tr>
<tr>
<td>• 6444 patients without sICH</td>
<td>• 465 patients without sICH</td>
</tr>
<tr>
<td>1.7% sICH rate; 95% CI = 1.4-2.0</td>
<td>8.6% sICH rate; 95% CI = 6.3-11.6</td>
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<tr>
<td>Mortality at 3 mo:</td>
<td>Mortality at 3 mo:</td>
</tr>
<tr>
<td>701 dead/6218 alive</td>
<td>83 dead/479 alive</td>
</tr>
<tr>
<td>11.3% mortality rate</td>
<td>17.3% mortality rate</td>
</tr>
</tbody>
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Abbreviations: CI, confidence interval; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institutes of Neurologic Disorders and Stroke; sICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*From Wahlgren et al.*

*SITS-MOST* used the new definition of sICH resulting in a 1.7% rate; when applying the sICH definition used in the original NINDS rt-PA Stroke Study, SITS-MOST rates increase to 7.3%.
that intravenous alteplase is safe and effective in routine clinical use when used within 3 hours of stroke onset.

**European Cooperative Acute Stroke Study–3**

In 2004, Hacke and colleagues combined and analyzed the data from 6 randomized trials and the pooled analysis, showing that a favorable outcome (odds ratio = 1.4) was achieved with tPA treatment between 3 and 4.5 hours from the time of stroke symptom onset and that treatment within this time period was not associated with higher rates of sICH or death. These findings provided the basis for the ECASS-3 study, a randomized, double-blind, controlled clinical trial of tPA treatment between 3 and 4.5 hours from symptom onset. The ECASS-3 study is largely regarded as the most important advancement in stroke care since the NINDS rt-PA Stroke Study. The study’s strengths include its multicenter, prospective, randomized, placebo-controlled design and significant sample size (tPA group, n = 418; placebo group, n = 403). Findings from the study include significantly more patients achieving excellent functional outcomes (scores of 0-1) on the modified Rankin Score (mRS) at 90 days in the treatment group (52.4% for tPA vs 45.2% for placebo; P = .04), an sICH rate of 2.4% (using the new sICH definition), and no difference in rates of death between groups. However, key aspects of ECASS-3 have sparked controversy about the generalizability of the findings.

The ECASS-3 excluded patients with a diagnosis of diabetes, those older than 80 years, and cases with severe stroke defined as an NIHSS score greater than 25 points. The current US FDA labeling for alteplase tPA does not exclude these patients from treatment within a 3-hour window, and the higher incidence of diabetes in the United States, particularly in the southeastern “stroke belt” region, makes the exclusion of these patients problematic. The exclusion of patients older than 80 years also raises concerns that in the near future there is the potential to exclude a large number of otherwise suitable thrombolysis candidates. The NINDS study did not specify an upper age limit, but only 42 patients older than 80 years were included. Consequently, our knowledge about the safety and efficacy of tPA therapy is limited for this age group. In the United States, the fastest-growing segment of the total population consists of those 80 years and older. The growth rate for this group is almost 4 times that of the total population. In fact, in the United States, this group now represents 10% of the older population and will more than triple from 5.7 million in 2010 to more than 19 million by 2050. Given the growth of this demographic, to withhold thrombolysis based solely on age could be deemed unethical, especially in the case of a highly functional octogenarian.

In addition, patients with severe stroke have poor clinical outcomes with high rates of death when left untreated, so although they were excluded from ECASS-3 to avoid the risk of trial failure as a result of the risk of imbalanced groups, little is lost by treating these patients with intravenous tPA. Other criticisms include a failure on the part of the ECASS-3 investigators to use perfusion imaging to determine penumbral tissue at risk; however, given issues associated with the validity of CT perfusion imaging and the difficulty in rapid attainment of magnetic resonance imaging, the use of simple noncontrast CT increases the generalizability of the study to a variety of practice settings that may lack multimodal CT and magnetic resonance imaging. Last, the ECASS-3 study used the new sICH definition; therefore, making comparisons between the NINDS rt-PA Stroke Study and the ECASS-3 study can be difficult. However, when the NINDS study’s definition is applied, ECASS-3 sICH rates increase to 7.9%, providing a glimpse of how these 2 trials compare to each other. Patients in ECASS-3 were allowed to receive parenteral anticoagulants for venous thromboembolism prophylaxis within 24 hours of intravenous alteplase administration, which might have contributed to their sICH rates, but overall, even using the NINDS sICH definition, 8 of 100 cases is an acceptable rate, given the benefits associated with the treatment.

**Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register**

A voluntary registry was established covering 700 centers around the world as a phase IV effectiveness study for intravenous thrombolysis between 3 and 4.5 hours from symptom onset. Called The Safe Implementation of Thrombolysis in Stroke-International Stroke
This registry has shown that the number needed to treat for just 1 patient to achieve a favorable outcome (mRS 0-1) was 14 but may, in fact, be reduced further to 10 needed to treat if comparing findings with baseline data profiles from multiple randomized clinical trials of tPA.28 By February 2010, the SITS-ISTR had recruited more than 30,000 patients and demonstrated clinical outcomes similar to those seen in clinical trials, with lower complication rates.27 Recently, an Australian study explored whether the increase in the time treatment window to 4.5 hours is associated with longer times to initiation of thrombolysis, finding that median time was 131 minutes in Australian SITS-ISTR registered patients.29 The Riks-Stroke Swedish stroke registry also found that following the release of ECASS-3 in 2008, thrombolysis in the 3- to 4.5-hour window increased from 0.5% to 2.1% by 2010 without a change in door-to-needle times, which remained unchanged at 66 to 69 minutes before and after 2008 (P<.06).30

Conclusions and Recommendations
Thrombolysis with intravenous tPA up to 4.5 hours from symptom onset in ischemic stroke has been adopted and supported in many parts of the world. Although it remains unclear whether the US FDA will approve a label change that incorporates the 4.5-hour time treatment window, those practitioners in the United States who have not endorsed this expanded treatment window and acted on the recommendations of the ASA have fallen sharply behind the rest of the world, drawing into question their advocacy for reperfusion therapy. The real question that persists today is whether imaging can take the place of the clock and allow health care providers to make treatment decisions based solely on the integrity of brain tissue, regardless of when symptoms started.

Intravenous tPA Treatment of “Wake-up” Strokes
Clinicians who treat acute stroke commonly encounter patients admitted with stroke symptoms that started during sleep, with a “last time seen normal” that occurred sometime the evening or day before presentation to the emergency department. Often, these patients also have a normal noncontrast CT scan that does not show signs of ischemic damage. Further complicating this presentation is the fact that findings from vascular imaging with CT angiography may be negative in many of these cases, indicating that the cause is likely a small vessel occlusion that is not amenable to intra-arterial treatment.

Controversy 3: Should “Wake-up” Ischemic Strokes With Normal Noncontrast CT Scans (and Presumed Small Vessel Occlusion) Be Treated With Intravenous tPA?
Several studies have shown that approximately 16% to 18% of patients with ischemic stroke awaken with neurological deficits.31-34 In wake-up stroke (WUS), symptom onset is defined as the time last seen normal (LSN), usually the night before, making these patients ineligible for intravenous tPA by current US FDA on-label guidelines. However, the circadian variation found to be associated with stroke occurrence indicates that the peak time for stroke ictus is the early morning hours, before awakening.35-36 In fact, some researchers suggest that stroke onset while sleeping may actually result in awakening the patient from sleep as a result of activation of the sympathetic nervous system. If this is the case, then a significant number of patients each year may benefit from intravenous administration of tPA to reduce neurological disability.

Numerous studies have explored the feasibility and safety of administering intravenous tPA to patients presenting with stroke on awakening. Todo and colleagues31 retrospectively studied the noncontrast CT scans of 81 consecutive cardioembolic stroke patients. Computed tomography scans were assigned to 1 of 3 groups: time of onset less than 3 hours (n=46); WUS (n=17); and unknown time of onset (n=18). Reviewers were blinded to CT group assignment but were provided with the presenting NIHSS score; reviewers classified films as normal (without signs of acute injury) or early signs (signs of decreased attenuation, including loss of the insular ribbon, lentiform nucleus, and gray-white interface). Interestingly, CT reviewers found no difference between CT findings in patients admitted within 3 hours of symptom onset and WUS patients. However, definite hypodensities were significantly more common in patients with unknown time of onset compared with patients admitted within 3 hours (56% of unknown-onset patients vs 0 patients within 3 hours;
P < .001) and patients in the WUS group (56% of unknown-onset patients vs 11% of WUS patients; P = .012). Although the study was limited to cardioembolic stroke, it does identify that a significant number of WUS cases may present with CTs suitable to treat with intravenous tPA; however, lack of a standardized method for CT rating may have increased the risk of bias in this study.

Huisa et al analyzed CTs of prospective ischemic stroke patients arriving within 4 hours of symptom onset (control group) and WUS cases (defined as > 4 hours but < 15 hours from LSN, or those arriving between 4:00 AM and 10:00 AM), using the Alberta Stroke Program Early CT Score (ASPECTS), a valid and reliable 10-point scale with a score of 10 being normal, that evaluates early signs of ischemic changes within the middle cerebral artery (MCA) territory. Patients in the WUS group (n = 36) had mean ASPECTS scores of 9 ± 1.9, compared with mean scores of 9.8 ± 0.7 (P = .0019) in the control group (n = 83). ASPECTS of 8 to 10 were found in 89% of WUS compared with 95% of controls. Because the definition of WUS was quite broad, an even higher rate of ASPECTS of 8 to 10 could have been achieved with a better defined cohort.

Although these 2 studies identify the high likelihood of normal noncontrast CT findings in WUS, the largest cohort of WUS treated with intravenous tPA was studied by Barreto and colleagues, who examined safety and clinical outcomes after off-label thrombolysis, comparing their findings to patients treated within 3 hours of symptom onset. Inclusion criteria for WUS were neurologically intact when LSN before going to sleep, witnessed or self-report of deficits upon wakening, disabling neurological deficit suitable for tPA treatment, and hypodensity less than one-third of the MCA territory on noncontrast CT scan. Subjects meeting inclusions consented to receive reperfusion treatment by either intravenous tPA or intra-arterial treatment at the discretion of the stroke attending physician. Symptomatic ICH was defined as an increase of 4 or more points in the NIHSS in association with parenchymal hemorrhage on CT, and targeted clinical outcomes were defined as excellent (discharge mRS 0-1) or favorable (discharge mRS 0-2). Of 80 WUS cases, 46 (median NIHSS 16) received intravenous tPA, and 34 (median NIHSS 10.5) were not treated. The WUS cohort was compared with an additional 174 cases (median NIHSS 11) that received intravenous tPA within 3 hours of symptom onset. The sICH rate was 4.3% in the treated WUS group with a mortality rate of 15%; no sICH or mortality occurred in the untreated WUS group.

Among the patients treated within 3 hours, the sICH rate was 2.9% with a mortality rate of 10%. Among the patients with WUS treated with tPA, 14% achieved mRS 0-1, compared with only 6% of untreated WUS cases; 32% of cases treated within 3 hours achieved mRS 0-1. Favorable outcome (mRS 0-2) was achieved in 28% of treated WUS cases, compared with 13% of untreated WUS cases and 48% of cases treated within 3 hours of symptom onset. Despite the small numbers in this study, patients with WUS treated with tPA achieved better clinical outcomes, despite higher NIHSS scores at baseline with acceptable rates of sICH, than patients with WUS who were not treated with tPA.

Conclusions and Recommendations

Although findings from a large, randomized, controlled clinical trial are needed to determine the safety and efficacy of intravenous tPA treatment of WUS, practitioners should note that the finding of a normal noncontrast CT scan signals the likelihood of salvageable brain tissue that may benefit from reperfusion therapy. In the interim, clinicians should immediately refer patients with WUS with normal noncontrast CT to comprehensive stroke centers or seek telemedicine consultation to determine an appropriate treatment plan that may benefit patient outcomes.

Intravenous tPA Versus Intra-arterial Treatment of Acute Ischemic Stroke

Unlike the cardiology paradigm that has shifted to primary intra-arterial treatment to establish coronary recanalization, in acute ischemic stroke, use of intravenous, systemic tPA remains the standard of care for patients arriving within 4.5 hours of symptom onset. However, methods for extracranial and intracranial intra-arterial treatment have evolved to include a large arsenal of weapons capable of restoring blood flow.
Controversy 4: Similar to the Cardiology Paradigm, Should Intra-Arterial Treatment Replace Intravenous tPA as the Primary Strategy for Arterial Recanalization in Stroke Centers With This Capability?

Timely recanalization of occluded arteries and subsequent reperfusion of ischemic brain represent the holy grail of acute stroke treatment. However, the efficacy of intravenous tPA alone may be limited in a subset of patients with large artery occlusions. Proximal large artery occlusions account for between 20% and 40% of all ischemic strokes, producing significant morbidity and mortality associated with ischemic stroke. In addition, early complete recanalization rates for internal carotid artery (ICA) occlusions with intravenous tPA alone have been reported in only approximately 10% of cases, whereas complete recanalization rates of approximately 30% have been reported in proximal MCA occlusions. Results from the PROlyse in Acute Cerebral Thromboembolism (PROACT) II and the Multi Mechanical Embolus Removal in Cerebral Ischemia (MULTI MERCI) studies have demonstrated large artery complete recanalization rates for intra-arterial therapy (IAT) of 57% to 70%, compared with approximately 34% complete recanalization with intravenous tPA alone. Although successful recanalization is an important predictor of a good clinical response, other factors associated with IAT may adversely affect ischemic stroke outcome.

Currently, thrombectomy devices that extract clots are approved by the US FDA for their ability to remove arterial clots, but 3-month outcome data have yet to show that intra-arterial thrombectomy is associated with equivalent or superior outcomes than treatment with intravenous tPA. In addition, the risk for sICH with IAT ranges from 8% to 12%, making this procedure a higher risk therapy overall. A limited number of facilities are capable of providing IAT for acute ischemic stroke; thus, patient transfer with its inherent increase in time to treatment would be commonplace should IAT be deemed a more appropriate primary therapy than intravenous tPA. Provision of full-dose (0.9 mg/kg) intravenous tPA to all patients who meet treatment criteria is therefore recommended, and this pretreatment may soften large arterial occlusions and even establish some degree of partial recanalization that may buy time for patients who need IAT.

Appropriate patient selection for IAT is extremely important and can be initiated early without extensive multimodal imaging in any stroke center. Presence of a hyperdense artery sign on initial noncontrast CT is the hallmark of large artery occlusion in acute ischemic stroke. The sensitivity of hyperdense artery signs to predict large artery occlusion can be increased through the use of thinner CT slices (2.5 mm), which can quantify thrombus burden and enable accurate measurement of the thrombus length. Interestingly, when proximal MCA thrombus length exceeds 8 mm, intravenous tPA alone is unlikely to result in complete recanalization. Advanced practice nurses (APNs) in acute neurovascular practice should become proficient with CT interpretation, including the ability to recognize hyperdense arteries in the basilar, distal ICA, proximal A1 segments of the anterior cerebral arteries, and both the M1 MCAs and M2 sylvian fissure “dot” sign, as these findings suggest large artery occlusion that may need more than intravenous tPA. Patient clinical presentation is also associated with the presence of a proximal large artery occlusion that may require IAT rescue. Patients presenting with highly disabling symptoms associated with NIHSS scores greater than 10 are likely to have a large arterial occlusion that may require rescue by IAT following intravenous tPA.

Conclusions and Recommendations

Intra-arterial therapies should be considered for patients with large artery occlusion who have contraindications to intravenous tPA. In addition, for patients presenting with thrombus in the precerebral arteries (common carotids, internal carotids, vertebral arteries), the basilar and proximal MCAs, or tandem occlusions (ICA-MCA or ICA-MCA–anterior cerebral arteries occlusions), intravenous tPA should be administered if there are no exclusions. However, successful recanalization with intravenous tPA generally occurs within the first hour following the bolus, so if no improvement occurs by 30 minutes from bolus, transfer to a comprehensive stroke center and/or alerting the interventional neuroradiology team should be considered. Most commonly, IAT is performed up to 8 hours from the time of symptom onset for anterior circulation strokes.
and longer for posterior circulation strokes, which have a higher tolerance to ischemia, but typically neuroimaging guides determination of brain viability more than specific times from symptom onset.\textsuperscript{40} Magnetic resonance diffusion and perfusion mismatch carry the most reliable assessment of tissue viability, whereas CT perfusion imaging is evolving in its ability to validly and reliably predict brain tissue at risk.

Expanded Roles for APNs in Acute Stroke Management

A shortage of vascular neurologists in the United States has lowered intravenous tPA treatment rates in comparison with most European countries. This shortage has created an opportunity for APNs to play a critical role in the selection, treatment decision making, and ongoing management of patients with acute stroke.

Controversy 5: Can APNs Accurately Diagnose Acute Ischemic Stroke and Make Safe tPA Treatment Decisions?

Postgraduate Fellowship Preparation of APNs

Alexandrov and colleagues\textsuperscript{49} created a first of its kind postgraduate APN Acute Neurovascular Academic Fellowship program supported by funding from the Health Resources Services Administration in 2007. The Neurovascular Education and Training in Stroke Management and Acute Reperfusion Therapy-Advanced Practice (NET SMART-AP) program uses a hybrid Internet-based didactic/clinical training approach that partners APNs with local vascular neurologists, with the aim to train expert APNs capable of driving improved tPA treatment rates. Program content is evidence based and externally vetted by expert vascular neurologists. Advanced practice nurse fellows complete at least 1000 clinical practice hours and must pass written examinations as well as clinical skills testing to progress through the program. Learning activities culminate in an on-site clinical validation session whereby fellows’ knowledge and skills are validated by the program leadership.

NET SMART-AP program outcomes from the first graduating class demonstrated a significant increase in baseline tPA treatment rates, which averaged 3.3% on program entry at fellows’ practice sites and increased over a period of 1.4 years to an average of 11.6% at the time of program completion (paired \( t = 9.34\); mean difference = 8.3; 95% confidence interval [CI] = 6.4-10.2; \( P < .001 \)).\textsuperscript{50} Importantly, this increase in tPA treatment occurred with an average sICH rate of 4.4% (range, 2%-6.25%),\textsuperscript{50} well below the 6.4% sICH rate reported in the NINDS rt-PA Stroke Study.\textsuperscript{1} In addition, 100% of sponsoring vascular neurologists rated themselves as confident in their graduate fellows’ ability to appropriately select candidates for reperfusion therapy. Graduates’ pretest knowledge increased significantly by completion of the program (\( t = 12.2\); mean difference = 84; 95% CI = 70-99; \( P < .001 \)), and all graduates rated their overall confidence in role performance as significantly improved.\textsuperscript{51} NET SMART-AP program outcomes clearly demonstrate the power of using expertly educated and clinically trained APNs as a safe method to improve the rate of tPA treatment for acute ischemic stroke; however, for centers interested in developing and/or expanding their telemedicine coverage, little is known of the use of acute neurovascular APNs to cover telemedicine response for remote hospitals.

Advanced Practice Nursing Roles in Telemedicine

The term \textit{telemedicine} can be broadly defined as a way of providing medical services by means of phone, video, computer, or other electronic support.\textsuperscript{52} Telemedicine has been used for more than 40 years, beginning with psychiatry and radiology, and currently the term \textit{telestroke} is used to define a method for remote assessment, diagnosis, and treatment of patients with acute stroke that can greatly benefit communities that are underserved by vascular neurologists.\textsuperscript{53} Rural and urban community hospitals have an increasingly difficult time retaining on-call coverage for emergency stroke care by neurologists,\textsuperscript{54} and Stradling\textsuperscript{55} showed that the preimaging misdiagnosis of stroke by primary care or emergency physicians may be as high as 30% when compared with a specialized stroke team. Telemedicine can significantly increase intravenous tPA treatment rates when supported by expert vascular neurology teams. For example, Demaerschalk and colleagues\textsuperscript{56} noted that the baseline use of intravenous tPA treatment in rural Arizona was approximately 0.5 to 1.0 treatment per hospital, but with the initiation of
telemedicine, these investigators were able to achieve an average 30% intravenous tPA treatment rate in eligible patients.

An ever-widening gap exists between the small numbers of newly graduating vascular neurologists and the significant growth of the aging population with vascular risk factors for stroke. Moreover, hospital organizations are feeling pressure to become primary stroke centers under the watchful eye of increasingly savvy consumers. However, 77% of US counties are lacking neurology coverage, and neurologists who have completed fellowships in vascular neurology are even more limited. Further challenging patient access to vascular neurology are the daytime and on-call work requirements that went into effect in 2003 by the Accreditation Council for Graduate Medical Education, which limit medical resident and fellow availability. In addition, in 2011, the Joint Select Committee on Deficit Reduction (the “Super Committee”) was formed to recommend to Congress reductions in federal spending to be accomplished over the next 10 years, and Medicare reimbursement for graduate medical education, the primary source of graduate medical education funding in the United States, has been identified as an opportunity for spending reductions.

Nurse practitioner roles were created to aid with the rising cost of health care, the increasing health care manpower shortages and the misallocation of health care resources. Although the role of APNs in the diagnosis and treatment of acute stroke is relatively new, it is likely to grow significantly in the coming years in the face of significant vascular neurologist shortages and consumer demands for evidence-based acute stroke care. Recommendations for the interdisciplinary care of patients with ischemic stroke identify the role of APNs as key stroke team members who can facilitate evaluation and treatment, with APNs well tooled to take on various roles, including diagnosis, treatment, quality improvement, program coordination, and community outreach. In fact, Demaerschalk and colleagues demonstrated the value of APNs not only in the development and facilitation of a telestroke network but also in the remote patient management of telestroke patients. These investigators showed that a partnership between a NET SMART-AP educated/trained APN and vascular neurologists reduced response times by 10 minutes from initial call to completion of a neurology examination, and overall time to completion of the consult was reduced to approximately 12 minutes when working in partnership with a fellowship-educated APN, compared with an average 61 minutes when consulting alone.

Conclusions and Recommendations
Vascular neurologists are minimally available to provide the coverage required for stroke, but APNs are demonstrating their worth and growing in numbers that may be sufficient to fill the gap. With appropriate education in vascular neurology, APNs could safely provide consultations in stroke telemedicine and significantly improve tPA treatment rates, whether providing direct management or remote management by telestroke.

Positioning and Early Mobilization of Patients With Acute Stroke
Patients with neurological disabilities from acute ischemic stroke are at significant risk for complications, but as a vascular disease that is subject to varying degrees of hemodynamic compromise, the risk for neurological deterioration with early mobilization must be weighed against potential benefits associated with early mobilization.

Controversy 6: Should Patients With Acute Ischemic Stroke Have Routine Early Mobilization Initiated Immediately Upon Hospital Admission?
Positioning of the Head of the Bed in Hyperacute Ischemic Stroke Management
In acute ischemic stroke, intracranial pressure (ICP) is unlikely to increase in the initial 48 hours from stroke onset time for several reasons. First, stroke completion times vary significantly on the basis of local and systemic hemodynamics, ranging from minutes to days in some cases; because increased ICP is associated with massive brain edema in completed infarction, the occurrence of increased ICP during the hyperacute phase of management is unlikely to occur. Second, although stroke can occur at any age, patients older than 55 years generally have some degree of atrophy that lessens intracranial brain volume; in the event of infarction, increased ICP often does not occur because critical intracranial volumes are
not exceeded when brain edema occurs. Complete occlusions have been shown to be uncommon in large-artery acute ischemic stroke, with more than 80% of cases demonstrating some degree of residual blood flow through a narrowed intra-arterial lumen. Given these findings, most US vascular neurologists suggest that the head of the bed (HOB) should be kept at 0° (flat) in the first hyperacute 24-hour period to optimize residual blood flow to the ischemic brain.

“Heads down” was a repeated-measures quasi experiment that examined HOB positioning in patients with acute ischemic stroke because of proximal MCA occlusions who were not candidates for intravenous tPA by standard of care. Using transcranial Doppler, investigators measured arterial mean flow velocities (MFVs), demonstrating an increase in MFV as the HOB was taken from 30° elevation to 15° and subsequently 0° (flat) positioning. Although this study was small, the effect size for the intervention at 3 levels was 0.40 with a minimum r of 0.89 and an observed power of 0.85, demonstrating a significant increase of 20% in arterial MFV when the HOB was reduced to flat (0°) positioning. Interestingly, the investigators also noted 3 patients who developed profound improvement in neurological disability when placed at 0°.

Using cerebral blood flow measurement, Durduran and colleagues investigated the heads down phenomenon. These investigators found a similar 20% increase in blood flow when the HOB was placed at 0° (flat) from 30° elevation, but they also tested the use of Trendelenburg positioning, finding that blood flow in ischemic territories could be further increased with the head placed in a dependent position. Last, Hargroves and colleagues studied the influence of positioning on cerebral oxygenation after acute ischemic stroke, using near-infrared spectroscopy during position changes in 7 patients with MCA large-artery occlusions up to 7 days from stroke onset. A total of 6 of 7 patients demonstrated maximum tissue oxygenation index when placed in a 0° position, with a reduction in tissue oxygenation index noted in the 90° sitting position. Although these small studies provide theoretically sound evidence of improved blood flow associated with flat HOB positioning in ischemic stroke due to large-artery occlusions, it remains unclear whether flow can be augmented by HOB positioning in lacunar (small vessel) stroke. Furthermore, some researchers suggest that early mobilization may significantly improve outcomes of patients with acute stroke, challenging the benefit of 0° positioning.

Early Mobilization of Patients With Acute Stroke

The clinical support for very early mobilization (VEM) is based on findings from 1 site, the Trondheim Stroke Unit in Norway. In 1999, Trondheim investigators demonstrated that patients admitted to their stroke unit who practiced VEM were less likely to die and more likely to return home. In 100 patients with moderate to severe stroke admitted within 24 hours of stroke onset, 86% tolerated VEM by measurement of blood pressure (BP), oxygenation, and heart rate. Although transient changes in vital signs were noted most commonly within 5 minutes of position change, these disappeared by the end of the 55-minute VEM procedure. These investigators also noted improvements in level of consciousness and oxygen saturation during VEM.

Bernhardt and colleagues have postulated that because VEM has been used in Scandinavian hospitals with potential benefit and no clear signal of harm, methods for VEM should then be standardized and studied in other stroke units. Bernhardt leads the clinical trial called A Very Early Rehabilitation Trial (AVERT), which is under way at several international sites in Australia, Asia, and Europe. In AVERT phase I, Bernhardt and colleagues completed an open observational mapping study in Melbourne, Australia, that aimed to determine physical activity patterns of patients with stroke as a first step to develop an early mobilization protocol. Data showed that patients with acute stroke spend 53% of the day resting in bed, 28% sitting out of bed, and 13% in intentional physical activity, but that patients with acute stroke were alone more than 60% of the time.

The AVERT phase II safety and feasibility study commenced in 2004. In this randomized controlled trial with blinded outcome assessment, patients admitted who had stroke symptoms for less than 24 hours were randomized to receive standard care or VEM. In the target group, VEM was started within the first 24 hours and continued daily for 14 days or until discharge. At 3 months, 15.5% of subjects were dead, with more patients in the...
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in BP causes additional bleeding and subsequent enlargement of the hematoma.

Controversy 7: Should BP Be Aggressively Lowered in Patients With Acute ICH to Prevent Hematoma Expansion and Therefore Improve Clinical Outcome?

Hypertensive ICH is the most common type of ICH, typically occurring in the territory of the brain where the deeper penetrating arteries come off parent vessels at a 90° angle. These small penetrating vessels are affected by hypertensive occlusive disease and diabetic vasculopathy, making them vulnerable to rupture under cases of extreme hypertension. Small penetrating blood vessels in patients with chronic hypertension develop intimal hyperplasia and blood vessel wall degeneration; over time, these vessel changes lead to focal necrosis and, ultimately, blood vessel wall breakdown. The brain injury related to ICH is thought to be primarily related to ICH mass effect, which leads to local neuronal ischemia from decreased blood flow to the perihematoma area and subsequent accumulation of cytotoxic factors. Although the exact mechanism for hematoma expansion is not known, new bleeding likely occurs at the rim of the hematoma from stretching of surrounding vessels and successive vessel rupture, which leads to a breakdown in the blood-brain barrier and a cascade of inflammatory activation that disrupts hemostasis.

Greater than 50% of patients with ICH have a neurological deficit that deteriorates within minutes to hours and may possibly be accompanied by headache, nausea, vomiting, decreased level of consciousness, and elevated BP as the hematoma enlarges. Approximately 38% of patients experience maximum symptoms at ICH onset. Abnormally high elevation of BP occurs in up to 90% of patients with ICH and in some retrospective studies is also associated with hematoma expansion. Hematoma expansion is associated with a 5-fold increase in clinical deterioration, poor outcome, and death. On the basis of findings from the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) and Anti-hypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) safety and feasibility studies, the ASA published new guidelines...
suggesting that rapid aggressive lowering of systolic BP between 140 and 160 mm Hg is “probably safe.”

INTERACT compared aggressive lowering of systolic BP to 140 mm Hg with standard of care 180 mm Hg within 1 hour of admission and maintained for 24 hours. No true difference was found in hematoma expansion, although more aggressive control of BP leaned toward a reduced absolute growth from baseline.

ATACH studied the safety and feasibility of 3 BP-lowering tiers (tier 1: systolic BP 170-200 mm Hg, n = 18; tier 2: 140-170 mm Hg, n = 20; tier 3: 110-140 mm Hg, n = 22) in supratentorial ICH treated within 6 hours from stroke onset. Treatment failures were most common in the lowest BP tier; neurological deterioration, serious adverse events, and death were also most common in the lowest treatment tier, although not at rates that were statistically different from the other treatment groups. At present, it remains unclear whether aggressive early BP lowering prevents hematoma expansion and improves patient outcomes. Neurosurgery literature concurs that the best strategy for BP control is unclear, suggesting that rapid aggressive lowering of systolic BP may compromise cerebral perfusion pressure and potentially worsen brain injury, especially in the setting of increased ICP. Current guidelines recommend cerebral perfusion pressures between 50 and 70 mm Hg, although ICP is rarely measured acutely if at all in patients with primary hypertensive ICH. In addition, in patients with chronic hypertension, aggressive BP lowering can result in global hypoperfusion. Christiansen and colleagues noted that a decrease of less than 10% in systolic BP within the first 24 hours was significantly associated with less severe neurological impairment in a secondary analysis of the FAST trial. Similarly, Mayer and colleagues noted in the STAT registry (Studying the Treatment of Acute Hypertension) that death in neurological patients was associated with lower BP values and a reduced likelihood to experience recurrent hypertension.

Conclusions and Recommendations

In 2008, the Cochrane Collaboration concluded that insufficient evidence is available to determine the efficacy of BP lowering in ICH. The current INTERACT II study is expected to further define the association of intensive BP reduction with functional patient outcomes, whereas ATACH-II is evaluating the therapeutic effects of intensive BP reduction on death or disability at 90 days posttreatment among those treated within 3 hours of symptom onset. Together, these studies will significantly guide future practice recommendations, but until they are completed, practitioners will have to be satisfied with guidelines based primarily on expert consensus.

Summary

Stroke science continues to evolve, and as it does, clinicians’ knowledge of how best to respond to stroke emergencies is growing. Clinicians managing patients with acute stroke must diligently reflect on how to improve their practice by incorporating new scientific findings and networking with practice leaders to expand their thinking and approach to acute stroke treatment.

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