Tissue Plasminogen Activator and Time to Treatment

The National Institute of Neurological Disorders and Stroke studies,1 published in 1995, demonstrated for the first time that in patients selected by clinical and noncontrast computed tomography criteria, intravenous TPA (IV tissue plasminogen activator) resulted in improved outcomes compared with standard treatment. Since that time, safe and quick delivery of IV TPA has become the primary focus of acute stroke management and forever changed the way that acute stroke care is delivered.

The most important variable that predicts response to treatment is time from symptom onset to treatment initiation.2,3 On the basis of European Cooperative Acute Stroke Study III (ECASS III),4 treatment with IV TPA in Europe is approved out to 4.5 hours, but the benefit of treatment if started >3 hours is marginal if any. IV TPA is not approved >3 hours in the United States and best results occur if treatment is started within 2 hours. The number needed to treat of 3.1 within 3 hours5 is probably ≥2 if treatment is started within 2 hours. Recently, this lesson has been reinforced by the International Stroke Trial (IST),6 which once again confirmed that time is the most important determination of IV TPA benefit, and that other criteria, such as advanced age and increased stroke severity, commonly used to exclude patients from treatment, do not in fact preclude benefit.7 Although such a narrow time window necessarily limits treatment to only a subset of stroke patients, such is the reality of reperfusion therapy at least with IV TPA as demonstrated now by abundant human clinical trial data.

Because IV TPA was approved in 1996, this critical importance of time to treatment has generated a massive change in the way stroke is managed by prehospital emergency medical services (EMS) and emergency departments (EDs). Guidelines have promoted triage of all acute stroke patients to the nearest primary stroke center (PSC).8 More than 800 PSCs have been certified throughout the country.9 PSCs often enlarge their territory to include patients from treatment, do not in fact preclude benefit.7 Although such a narrow time window necessarily limits treatment to only a subset of stroke patients, such is the reality of reperfusion therapy at least with IV TPA as demonstrated now by abundant human clinical trial data.

Need for Better Treatments, Especially for Severe Strokes

As if the narrow time window were not enough of a problem, the other deficiency of IV TPA therapy is that it does not work well enough, particularly for larger arterial occlusions. Only 1 in 3 of all patients treated with IV TPA within 3 hours of symptom onset will return to a modified Rankin score of 0 to 1 (ie, no disability).4 Of patients with proximal middle cerebral artery occlusions, only 15% to 20% will recanalize by 2 hours after TPA bolus, and this number is lower for proximal or distal carotid or basilar occlusions.11 On the other hand, 70% to 75% of patients with less severe strokes (National Institutes of Health Stroke Scale <5) will recover without disability whether or not they receive IV TPA.6,10

There are a number of strategies under investigation to improve on what can be achieved by IV TPA alone. These strategies include adding therapies to IV TPA to increase the rates of quick recanalization, in particular using extracranial ultrasound, antithrombotic devices and intra-arterial lytics, or neuroprotective strategies (eg, hypothermia, magnesium); better stroke unit and neurocritical care management (eg, glucose control, blood pressure management, hemicraniectionomy); and efforts to promote stroke recovery (eg, activity-based therapy, robotics, cell-based therapies). Although this review concerns ischemic stroke, it must be added that better treatments are also needed and are under evaluation for hemorrhagic stroke as well.
unit. Although the elements of stroke unit care that result in improved outcomes are unknown and may be particular to European centers, it is likely that they include earlier rehabilitation, multidisciplinary attention, better recognition and treatment of stroke comorbidities, prevention and treatment of common stroke complications, and quicker institution of secondary stroke prevention. Recently it has become appreciated that there is a need for a hierarchy of stroke centers that provide more than the basic stroke unit care, especially for more severe stroke patients. This year comprehensive stroke centers (CSCs) will be certified for the first time. CSCs contain more in-depth vascular neurology expertise, trained nurses and therapists, neuroradiology expertise, endovascular therapy, timely neurosurgical intervention in selected patients, and critical care management. In particular, recent data with the newest generation stent-retrievers demonstrate an order of magnitude faster ability to achieve recanalization of larger clots. These latter components are not available in most PSCs, and 1 study from Europe has shown that CSCs containing all these components result in better outcomes and lower mortality compared with PSCs. Furthermore, in addition to providing more in-depth specialized care, CSCs will be required to carry out research. Finally, in Houston, CSCs treat 12% of stroke patients they see (90% of those TPA eligible) compared with 7% and 76% for PSCs.

### Declining Percentage of Patients With Severe Strokes Are Being Taken Directly to CSC EDs

Current guidelines for EMS are to take patients to the nearest stroke center, without distinguishing between PSCs and CSCs. With the proliferation of PSCs throughout the country, it is likely that a declining percentage of stroke patients are being seen initially at CSC EDs. Recent analyses from our own CSC show that from 2005 to 2011, the proportion of our stroke admissions resulting from direct delivery of the patient to our ED by EMS has declined from 75% to 55%, whereas the number of patients transferred to us from PSCs or nonstroke centers has increased from 166/year to 534/year (presented as abstract at 2012 American Heart Association International Stroke Conference). Although the development of PSCs has resulted in more patients getting treated, the effects of this redirecting of patients to PSCs may not all be positive. Just because a patient is transported to a PSC more quickly than to a more distant CSC does not mean they will be treated faster because door to needle times in the CSC may be faster. Door to needle time, or EMS arrival to needle time, are important quality assessments that need to be established for both PSCs and CSCs. More importantly, however, is that severe stroke patients who may benefit most from CSC care are not coming directly to CSC EDs. Again, data from our own center show a decline in the proportion of patients with large artery strokes (33%–22%), an increase in those with minor strokes (37%–49%), and a consequent decline in the percentage of patients enrolled in acute stroke clinical research studies focused on improving arterial recanalization (46%–19%), in direct proportion to the proliferation of PSCs in the surrounding areas (2–15) between the years 2005 and 2011. All the elements and relationships for these trends are unclear. For instance, it is possible that this reflects an increase in the recognition and transport of less severe strokes to PSCs as well, but it is possible that paramedics are taking the more obvious strokes (ie, severe strokes) to the nearest hospital, which is usually a PSC, whereas sending the more questionable cases (ie, less severe strokes) to the CSC to figure out.

### Case for a Severity-adjusted Stroke Triage System

So there is a dilemma in prehospital stroke care. Patients need to be treated absolutely as fast as possible, but severely affected stroke patients are better off going to CSCs that may require longer transport. This is not a new dilemma in medicine. Obvious parallels exist in trauma and coronary artery disease, the other 2 conditions of similar urgency to acute stroke. A trauma center hierarchy has existed since the 1970s, and state legislation supported by the American College of Surgeons and Centers for Disease Control and Prevention mandate that severe trauma patients to be taken to a level 1 trauma center, with proportionately less severely affected patients to lower-level centers. Similarly, patients with ST-segment–elevation myocardial infarcts are usually triaged to centers with cardiac catheterization capability. It is only logical that we adopt a similar system for stroke patients. The presence of a large artery occlusion (and a larger more life-threatening intracerebral hemorrhage) is proportional to the stroke severity as measured by the National Institutes of Health Stroke Scale. Recently, the Los Angeles Motor Scale, a brief stroke severity assessment scale designed for prehospital and ED use, was shown to be valid to predict large artery occlusion with sensitivity, 0.81; specificity, 0.89; and accuracy, 0.85, if the score was >4. This 3-item score, consisting only of face, arm, and grip strength has been used successfully by paramedics to convey stroke severity information in the Field Administration of Stroke Therapy—Magnesium trial (FAST-MAG; ClinicalTrials.gov NCT00059332).

### Proposed Severity-adjusted EMS Triage Algorithm

We propose a severity-adjusted EMS triage algorithm that takes into account stroke severity and the likelihood of a patient harboring a large artery occlusion (or large intracerebral hemorrhage) that would benefit from urgent CSC care, while at the same time preserving the urgency to treat patients as fast as possible (Figure 1). Although a prospective study comparing various triage schemes would be ideal, regional variability in stroke care logistics probably requires a system tailored to local needs. For instance, in small communities with limited EMS resources, long transport times, such as our proposed cutoff of 40 minutes for specific patients, would limit the availability of an ambulance for other patients in need. The Centers for Disease Control and Prevention Field Triage “Guidelines for the Field Triage of Injured Patients” recommends transport (of severely injured patients) to a facility that provides the highest level of care within the defined trauma system. For Houston, ground transport to the nearest level 1 trauma center from anywhere within our defined trauma system covered by EMS could take up to 40 minutes. This time might differ for defined
Proposed EMS acute stroke triage criteria

LAMS

- Face weak
  - Absent 0
  - Present 1
- Arm weak
  - Absent 0
  - Drift 1
  - Falls rapidly 2
- Grip strength
  - Normal 0
  - Weak 1
  - No grip 2

1 or 2 points goes to the highest center within 20 minutes (likely a minor stroke that could get tPA at any stroke center and probably would not be a candidate for more aggressive therapy).

3-5 points, or any patient who is drowsy or has impaired consciousness, goes to a CSC regardless of how long it takes (these are more severe strokes that would benefit from a higher level of care). If ground transport to a comprehensive center would require more than 40 minutes, then air transport should be considered.

EMS Systems should promptly notify receiving facilities in order to allow for timely facility-specific stroke team alert mechanisms to be activated.

Figure. Proposed sample severity-adjusted EMS triage algorithm. CSC indicates comprehensive stroke center; EMS emergency medical services; LAMS, Los Angeles motor scale; and tPA, tissue plasminogen activator.

Disclosures

Drs Grotta and Savitz report a conflict of interest with a National Institute of Health research grant >$10,000. The other authors have no conflicts to report.

References


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