

MYOCARDIAL INFARCTION & ISCHEMIA THERAPY UPDATE

Thrombolysis for Acute Ischemic Stroke: a New Paradigm

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KEY WORDS: *stroke; thrombolysis;
cerebral perfusion; stroke units*

ABBREVIATIONS

CT = computed tomography
INR = international normalized ratio
rt-PA = recombinant tissue-plasminogen
activator

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ABSTRACT

Modern day therapy of acute ischemic stroke is based upon intravenous thrombolysis, which has altered management of this potentially devastating disease. The urgent treatment of acute ischemic stroke must be of the same priority as the treatment of acute myocardial infarction. Specific networks must be established to ensure rapid transfer of stroke patients to designated hospitals that have the resources in place to deliver thrombolysis. Prior to the initiation of any treatment, diseases that mimic strokes must be ruled out. Prompt completion of computed tomography (CT) scanning should be performed to rule out hemorrhagic stroke and determination of the severity of the stroke using the various grading scales should be made. Recombinant tissue-plasminogen activator (rt-PA) is the only thrombolytic agent currently approved by the FDA for ischemic stroke treatment. It must be initiated within 3-4.5 hours of symptom onset. The extent of the difficulty in establishing the goals outlined above is evident from the observed low rate of thrombolysis. Even in the US, the proportion of stroke patients being thrombolysed does not exceed 3.5%. This is primarily due to patient delayed presentation. However, the goal of initiating thrombolysis as soon as possible, to maximize the potential for benefit, should be strongly encouraged.

INTRODUCTION

Cerebrovascular accidents or strokes continue to represent a serious health problem with significant associated morbidity and mortality and remain the third leading cause of death following cardiac diseases and cancer. In the US, 795,000 new strokes are diagnosed annually and result in 150,000 deaths. In patients over 65 years of age, 25% remain disabled after 6 months resulting in a significant economic burden on health resources.¹

In accordance with the World Health Organization, stroke is defined as a clinical syndrome characterized by rapid onset of symptoms due to regional neurological deficits (at times global) that last more than 24 hours or result in death, with no obvious cause other than a vascular etiology.² Stroke can be classified as ischemic (85%) or hemorrhagic (15%), with a small percentage (0.5-1%) involving the cerebral veins. Ischemic stroke results from either local thrombosis with occlusion of a cerebral artery, or embolism arising from the heart, aorta or a carotid artery. A total of 20-25 %

of ischemic strokes are of cardiac etiology, primarily due to atrial fibrillation.

The region of ischemic tissue surrounding the infarction core is referred to as the “ischemic penumbra”. This ischemic region is dysfunctional but free of permanent damage and with reperfusion, function rapidly returns. From primate research models, it has been determined that regional neurological symptomatology appears when cerebral blood flow falls below 23 ml/100 gm tissue/min and permanent damage occurs with blood flow below 10-12 ml/100 gm tissue/min.³ Therefore, our efforts are directed at rapidly reestablishing perfusion of the ischemic penumbra.

THROMBOLYSIS

In recent years, thrombolytic therapy has altered management of acute ischemic stroke from nihilism to an active intervention. The urgent treatment of acute ischemic stroke must be of the same priority as the treatment of acute myocardial infarction. The rule, lost time equals lost brain, must predominate in the thoughts of all who are involved in the transfer, receipt and treatment of stroke patients. This is why specific networks must be established to ensure rapid transfer of stroke patients to designated hospitals that have the ideal resources in place, bypassing those that do not.⁴ In other words, there must be specialty centers and stroke units that have established protocols for rapid diagnosis, admission, and patient treatment. Protocol goals include completion of the assessment within 60 minutes. Modern day therapy of acute ischemic stroke is based upon intravenous thrombolysis and intravascular treatments that include intra-arterial thrombolysis, mechanical clot removal and angioplasty with stent insertion. The extent of the difficulty in establishing the goals outlined above is evident from the observed low rate of thrombolysis. Even in the U.S., the proportion of stroke patients being thrombolysed does not exceed 3.5%. This is primarily due to patient delayed presentation. If however, all patients were routed through an established emergency network, the percentage would increase to 30%. Furthermore, if all patients presented within the first hour of symptom onset, more than half would be eligible for thrombolytic therapy.⁴ In specialty stroke units, the percentage of thrombolysed patients increased to approximately 10% with a significant decrease in mortality up to 50%.

Prior to the initiation of any specific treatment, diseases that mimic cerebrovascular accidents such as conversion disorder, hypertensive encephalopathy, hypoglycemia, complicated migraine, seizures and tumor, must be ruled out. Such disorders account for 13-31 % of presenting cases.^{5,6} Also, completion of computed tomography (CT) scanning should be performed to rule out hemorrhagic stroke and determination of the severity of the stroke using the various grading scales should be made. The time goal for the completion of and

interpretation of the CT should be no more than 45 minutes.⁴

Recombinant tissue-plasminogen activator (rt-PA, alteplase) is the only thrombolytic agent currently approved by the FDA for ischemic stroke treatment. It must be initiated within 3 hours of symptom onset and the dose is 0.9 mg/kg to a maximum dose of 90 mg; 10 % of the total dose is given initially over 1 minute and the remainder infused over 60 minutes (Tables 1 & 2). Hemorrhagic stroke is the major complication of thrombolytic therapy. Risk factors include older age, high blood pressure, diabetes, and the severity of the stroke. At this time there is insufficient data to justify the use of thrombolytic therapy in patients >80 years of age.

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study established the indication for thrombolytic therapy in ischemic cerebrovascular accident. Patients who received rt-PA had a 30% higher probability of complete or nearly complete neurological recovery at 3 months as compared to the patients who received placebo.⁷ While the rt-PA group suffered more symptomatic intracranial bleeds (6.4% vs. 0.6%), overall rt-PA resulted in a significant net benefit. The benefit observed with thrombolysis persisted at 1 year.⁸ Better prognosis was observed in patients with strokes of moderate severity, younger age and in those who received thrombolytic therapy within 90 minutes. At the same time,

TABLE 1. Indications and Contraindications of Intravenous Thrombolysis in Acute Ischemic Stroke

1. Moderate severity ischemic stroke.
2. Exclusion of hemorrhagic stroke.
3. Initiation within 3 hours of symptom onset.
4. No history of stroke within the last 3 months and no history of hemorrhagic stroke.
5. No history of myocardial infarction within the last 3 months.
6. No active bleeding nor history of bleeding within the last 3 weeks.
7. No anticoagulant use. If on anticoagulant, INR <1.7.
8. Blood pressure <185/110.
9. Platelet count >100,000 mm³.
10. No bleeding or clotting disorder.
11. No brain tumor, structural CNS disease nor history of significant head injury within the last 3 months and no history of major surgery within the last 2 weeks.
12. No serious systemic disease such as severe renal and hepatic dysfunction and terminal cancers.

CNS = central nervous system; INR = international normalized ratio

TABLE 2. Acute Ischemic Stroke: Arterial Hypertension and Intravenous Thrombolysis

1. If blood pressure <185/110 mmHg administer rtPA at a dose of 0.9 mg/kg over 60 minutes (10% as a bolus over 1 minute). Maximum dose 90mg.
2. If blood pressure >185/110 mmHg administer
 - a. Nitroglycerine IV, or
 - b. Labetalol IV, or
 - c. Nicardipine IV
3. If blood pressure does not decline below 185/110 mmHg, thrombolysis is contraindicated
4. Measure blood pressure every 15 minutes over the first two hours, then every 30 minutes for 6 hours and then every hour for 16 hours

other studies with different dosages and longer time windows (up to 6 hours) failed to show a benefit but did show a greater number of intracranial bleeds (ECASS-I, ECASS-II, Atlantis).⁹⁻¹¹

The indications and contraindications for treatment with thrombolytics for acute ischemic stroke are the same as those identified for the treatment of acute myocardial infarction (Table 1).⁴ It is emphasized that criteria for thrombolysis include initiation within the first 3 hours from the time of symptom onset, INR must be less than 1.7 in patients taking anti-thrombotic medications, and systolic blood pressure must be <185 mmHg and diastolic blood pressure <110 mmHg. If blood pressure is $\geq$ 185/110 mmHg, anti-hypertensive treatment should be given to achieve permissible blood pressure levels (Table 2). If blood pressure targets are not achieved, thrombolytics must not be given.

In 2008 the results of ECASS III were published and revealed benefit of thrombolytic therapy when given between 3 and 4.5 hours after the onset of symptoms.¹² Also in 2008, a separate study revealed the same benefit for thrombolysis given within 3 to 4.5 hours as compared to the results for those treated within the first 3 hours.¹³ In 2009, following the results of these two studies and in particular those of ECASS-III, the American Stroke Association/American Heart Association extended the time limit for thrombolysis to 3-4.5 hours except for patient groups excluded from the study: patients >80 years of age, patients with severe stroke (NIHSS >25), patients on antithrombotics irrespective of INR, and patients with a history of cerebrovascular accidents with diabetes.¹⁴ However, the goal of initiating thrombolysis as soon as possible, to maximize the potential for benefit, should not be abandoned. It appears that thrombolysis has better results when the occlusion involves the middle cerebral artery as compared to the internal carotid artery where other therapies must also be considered.¹⁵ It is

probable that the difference in outcome is related to thrombus mass which is greater in the internal carotid artery.

The combination of thrombolysis and high frequency transcranial-doppler appears to have better results than lone thrombolysis.^{16,17} Intra-arterial thrombolysis requires a specialized center and is indicated in patients with occlusion of the middle cerebral artery <6 hours who are not appropriate candidates for intravenous thrombolysis (Class IB), or in those who have contraindications to intravenous thrombolysis (e.g. recent surgery) (Class IIa C).⁴ The indications are based upon findings of the PROACT II study, in which pro-urokinase given to patients with occlusion of the middle cerebral artery <6 hours after symptom onset revealed significant improvement in neurological function at 3 months (40% vs. 25%). However, there was an increase in intracranial bleeds (10% vs. 2%).¹⁸ At this time, this treatment is not recommended as a routine practice and awaits the results of the SYNTHESIS trial.

Initiation of treatment with heparin and aspirin in the first 24 hours following thrombolytic therapy is contraindicated due to increased risk of intracranial bleeds.⁴ Aspirin should be given to all patients with acute ischemic stroke after the first 24 hours unless the patient has contraindications. Clopidogrel alone or in combination with aspirin is not indicated in the treatment of acute ischemic stroke.⁴

There continue to be multiple unanswered questions related to thrombolytic treatment in acute ischemic stroke that require the completion of large randomized studies. Also, considerable efforts need to be made in order to establish the networks and specialized treatment centers required for handling of stroke patients, as has been accomplished for patients with acute myocardial infarction. Just very recently, the new thrombolytic agent, tenecteplase (TNK), which is currently routinely employed in acute myocardial infarction, was also tested in patients with acute ischemic stroke at two doses (0.1 and 0.25 mg/kg) and was found to be associated with significantly better reperfusion and clinical outcomes (particularly the higher dose) than alteplase (rtPA) in patients with stroke who were selected on the basis of CT perfusion imaging.¹⁹ The higher dose of tenecteplase (0.25 mg/kg) was superior to the lower dose of TNK and to alteplase for clinical efficacy (in 72% of patients, vs. 40% with alteplase; $P=0.02$), with no significant differences in intracranial bleeding or other serious adverse events.

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