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Foundation for the Education and Research in Neurological Emergencies (FERNE) Symposium

New Frontiers in Ischemic Stroke Therapy

Key Clinical Concepts

Thrombolysis and Beyond: The New Therapeutic Horizons for Acute Ischemic Stroke

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- The purpose of thrombolysis or clot retrieval in the setting of ischemic stroke is to dissolve or remove the clot in order to preserve the ischemic penumbra and minimize the size of tissue infarct.
- By minimizing infarct size, the NIHSS deficit measured acutely (and long-term in clinical trials) and the MRS and BI disabilities measured long term can be minimized, improving patient outcomes.
- In the NINDS clinical trial, there was a 14% absolute increase in the number of patients who had the best clinical outcomes as measured by an NIHSS of 0-1. This corresponds to a number needed to treat with tPA of eight patients in order to have one additional patient with this best outcome. This is associated with an extra patient with a significant ICH for every 16 patients treated with tPA, or one significant ICH patient for every two patients who have the best clinical outcome.
- In general, tPA should be considered to be optimally useful by reproducing the NINDS protocol, which studied tPA in patients with a median NIHSS score of 14, signifying a moderate stroke.
- Although tPA has never been demonstrated to be superior or inferior in patients with an acute NIHSS score of 0-5 (mild stroke) or greater than 20 (severe stroke), these stroke patients require a more careful assessment of the risks and benefits of tPA, given that they are less like the patients most commonly treated in the NINDS clinical trial.
- The independent reanalysis of the NINDS tPA clinical trial confirms the results from the initial *NEJM* publication, which support the use

- of tPA in stroke patients within three hours of symptom onset. the number needed to treat calculation based on this reanalysis confirms that approximately 8-10 patients need to be treated with tPA in order to cause one extra patient to have the best clinical outcome.
- A reanalysis of the NINDS clinical trial data regarding ICH provides to the emergency physician a list of risk factors that are correlated with the occurrence of a significant ICH. These risk factors include: baseline NIHSS > 20, age > 70 years, ischemic changes present on the initial CT, and glucose > 300 mg/dl (16.7 mmol/L). This information may assist in determining the risk/benefit ratio in the individual stroke patient.
 - Within three hours of symptom onset, IV tPA is the thrombolytic therapy of choice. Between three and six hours, there may be a role for intra-arterial tPA in institutions that provide this therapy, especially when the stroke is related to occlusion of the middle cerebral artery.
 - After six hours from stroke symptom onset, data suggests that posterior circulation strokes may benefit from attempts to provide thrombolytic therapy, but this data is limited in its scope.
 - Neuroprotectants are designed to minimize neuronal cell death and limit infarct size through penumbra stabilization. A recent *NEJM* publication demonstrated benefit in stroke patients with the use of a novel neuroprotectant. If confirmed in an ongoing second complementary clinical trial, this would represent the first clinically effective neuroprotectant.

The Diagnosis and Treatment of Acute Ischemic Stroke: New Frontiers in Managing ED Stroke Patients

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- The diagnostic modalities that are to be considered in the ED evaluation of stroke patients include: Cranial CT, CT angiography, MRI (including diffusion and perfusion weighting studies), MR angiography, cerebral angiography, carotid Doppler ultrasonography, and cardiac echocardiography.
- The treatment modalities for ED stroke patients include: IV and intra-arterial thrombolysis with tPA and other thrombolytics, clot retrieval, cerebrovascular stenting, and operative intervention, including carotid endarterectomy.

- A “double play” is the term used to describe the use of a clot retrieval device followed by the use of intra-arterial tPA to avoid downstream clots from causing further CNS injury. A “triple play” is the above two interventions with carotid artery stenting provided for critical carotid artery stenosis.
- The initial CT is performed in order to determine the presence of intracranial hemorrhage, a space-occupying lesion, signs of cerebral edema, and evidence of a large MCA distribution infarct or one of many hours’ duration.
- Although MRI can detect hemorrhage acutely and can provide information regarding the stroke pathology via diffusion/perfusion mismatch data, CT is still currently indicated in ED stroke patients, given its availability and its ability to support decision making regarding acute IV tPA therapy.
- Although cardiac echocardiography and carotid Doppler evaluation will determine the etiology of suspected thromboembolic strokes, neither is clinically indicated in order to assess the utility of IV tPA in the ED.
- Cerebral angiography, CTA, and MRA are utilized to detect the presence of intracranial vascular occlusions and/or vascular abnormalities that assist in defining the etiology of the cerebrovascular accident. Cerebral angiography is the test that will be performed acutely in the setting of planned interventional radiography techniques that include cerebrovascular stenting, mechanical clot retrieval, or intra-arterial thrombolytic therapy.
- Advanced diagnostic and therapeutic tests are indicated when the three hour IV tPA window has expired, if mechanical interventions or intra-arterial thrombolytic therapy is planned, or when the diagnosis of stroke or the etiology remains uncertain following the initial CT.
- These advanced therapies, although potentially beneficial to stroke patients, are neither universally available nor are the current standard of care. They are to be considered when available and feasible to provide, and when they are believed to represent an opportunity for improved stroke patient outcome.